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CONTENTS

ENZYMES FROM THE STANDPOINT OF THE CHEMISTRY OF INVERTASE

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The name invertase, or sucrase, is applied to any enzyme which catalyzes the inversion of cane sugar. Although the chief source of invertase is ordinary brewer's or baker's yeasts, it occurs widely spread in nature, being present in the tissues and fluids of many plants and animals. In most instances, however, it occurs only in small amounts, and often it is difficult or impossible to separate it even in a crude form from these tissues and fluids. For this reason, most studies of this enzyme have been carried on with invertase preparations obtained from yeast, from which it can be obtained in relatively large yields with a minimum amount of labor. The reason why invertase has been studied probably more than any other enzyme is because of its stability judged from the constancy of its activity, and because its substrate, sucrose, is a relatively simple substance as substrates go and has only one linkage which is affected by the enzyme.

Several methods have been employed in obtaining the enzyme from yeast. Some of the earlier investigators (4, 91) first dried the filtered yeast at about 100°C. so as to render the accompanying proteins more insoluble, and then extracted the dried material with water. Emil Fischer (30, 31) dried the yeast at about room temperature and extracted with water containing an antiseptic such as toluene. Others (49, 64) ground the pressed yeast with sand and then extracted with water saturated with chloroform.

Permitting the yeast to autolyze and then working up the liquid autolysate is the method mostly used at present. Among the first to employ this method were O'Sullivan and Tompson (88) in their excellent study of the enzyme. They allowed the pressed

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yeast to stand, at room temperature, until the yeast cells died and partially liquefied.   Hudson (41) improved greatly upon the procedure of O'Sullivan and Tompson by adding cell poisons, especially toluene (although he also tried others like ethyl acetate and chloroform), to the yeast.   In this way he was able to cut down the time required for the autolysis to a few days.

In preparing the crude invertase from the autolysate, Hudson first removed a considerable quantity of the accompanying soluble protein and gums by precipitating with lead acetate and removing the excess lead by means of potassium oxalate and subsequent dialysis.   The crude enzyme was then precipitated from the resulting solution by the addition of an equal volume of alcohol, and was finally redissolved in water.   Euler (16, 18) and his coworkers, however, found that the lead treatment is not essential, and that just as active preparations can be obtained by precipitating the original filtered autolysate with alcohol, extracting the precipitated protein and enzyme material with water, or dilute alcohol, and repeating the alcohol precipitation.

By assuming invertase to be a true chemical compound whose activity is directly proportional to its concentration, it becomes possible to measure the amount of the enzyme contained in a given weight of material, or in other words, the degree of purity of the enzyme preparation.   O'Sullivan and Tompson determined the number of minutes required by 50 milligrams of a preparation to hydrolyze to zero rotation at 15.5°C., 25 cc. of solution containing 16 per cent of sucrose and 0.5 cc. of acid sodium phosphate.   According to this measure or time-value, ordinary brewer's yeast runs from 150 to 400 minutes per 50 milligrams of yeast cells.   By means of the alcohol treatment of yeast autolysates, followed by subsequent treatment with kaolin to remove more of the extraneous proteins, Euler and Svanberg (19) succeeded in obtaining an invertase preparation which had a time-value of only 3.6 minutes.   At the time, this was probably the most active or highly purified invertase preparation ever obtained.

Since then, Willstätter and coworkers (109, 118) have succeeded in obtaining preparations having time-values as low as 0.1

minute, or 36 times more active than that prepared by Euler and Svanberg in 1919. The German chemists modified the Hudson method of rapid autolysis by what they termed fractional autolysis. The latter consists mainly in interrupting the autolysis two or three hours after the toluene or chloroform has been added to the yeast, filtering, discarding the filtrate, which usually contains very little of the enzyme, and finally again adding 10 per cent of toluene and two volumes of water to the residue and permitting the autolysis to proceed to completion.

Still another modification of Hudson's method used by the Munich workers is what is known as neutral autolysis. In the ordinary Hudson method for autolysis, the autolysate tends to become quite acid, the pH ranging from 4.0 up to 5. Willstätter and his associates reasoned that this high acidity might disturb the proteolytic enzymes involved in the liberation of the soluble invertase from the yeast protoplasm. Therefore, in some of their work, they kept the autolysis mixture neutral by means of either dilute ammonia or diammonium phosphate. They also state (110) that straight acid autolysis is apt to yield invertase preparations from which subsequently it is difficult to remove accompanying material that responds to the Millon test for proteins. Neutral autolysates, therefore, yield preparations which show only a faint Millon reaction. On the other hand, these investigators claim that acid autolysis has the advantage over the neutral of yielding preparations entirely free from tryptophan. Their best preparations obtained by means of the neutral method contained about 3 per cent of this amino acid. Preparations fully as active as those reported by the German workers, and made in the writer's laboratory either by the acid or neutral autolysis of yeast, all gave positive tests for the presence of tryptophan.

Probably the most outstanding contribution to the chemistry of invertase made by Willstätter and his students is the use of adsorption in the purification of the enzyme. The fact that enzymes can be adsorbed to other substances is not new. As far back as 1861 Brücke (7) and others adsorbed invertase from its aqueous solutions to colloidal matter like calcium phosphate, cholesterin and lecithin. About 1907 Michaelis (64, 67), in trying

to determine whether invertase was acid or basic in character, noticed that the enzyme was adsorbed to basic substances like ferric hydroxide and alumina, but not to more acid substances such as kaolin. This led him to use kaolin for removing extraneous protein matter present in the invertase solution, much in the same manner as that subsequently employed by Euler and Svanberg, as mentioned above. Willstätter and Racke were the first, however, to take up the subject of the adsorption of invertase in a systematic and thorough manner. They studied not only the influence of the age of the autolysate, but also the concentration of the enzyme, etc., on the extent of the adsorption of invertase to alumina. They also made an elaborate study of the form or state of the alumina best suited for the purpose (50, 51) and of the conditions as well as the reagents most suitable for the subsequent elution of the invertase from the adsorbent. In the case of kaolin (117) they found, contrary to the claims of Michaelis, that invertase can be adsorbed to this material provided that the solution is sufficiently acid and dilute.

The procedure usually followed by the Munich workers is first to subject the autolysate to a pretreatment, such as dialysis, or removal of some of the extraneous matter with lead, as done by Hudson, or more often precipitation with alcohol and dialysis. After the pretreatment, the solution is acidified by dilute acetic acid, the invertase is adsorbed to kaolin and eluted by means of dilute ammonia, sodium carbonate, or phosphate, and the resulting solution is dialyzed. The pH of the dialyzed solution is next adjusted to between 5 and 6, the invertase is adsorbed to alumina and eluted by means of disodium phosphate or arsenate, and the resulting solution is dialyzed. The alumina treatment is often repeated three to four times, when a solution is obtained containing very active material, judged by its low time-value. The kaolin adsorption usually removes most of the yeast gum which always occurs together with the invertase in its cruder preparations, while the alumina tends to remove nitrogenous matter. The accompanying outline illustrates the procedure followed by the Munich workers in the case of one of their most active preparations.

Fresh Autolysate (100)
Chloroform neutral autolysate (room temperature) no fractionation
Time-value of autolysate = 90 to 140 minutes
↓
Alcohol precipitation and extraction of the precipitate with $M/50$ acetic acid
Time-value 15 to 30 minutes
↓
Kaolin adsorption (1 unit in 500 cc. of $M/50$ acetic acid). Concentrating the
solution after elution and removing some of the protein precipitated by means of
sulfuric acid.
Time-value = 1 minute
↓
Repeated alumina adsorptions (2 to 4 times) with fractionation[1] from neutral or
very weakly acid solutions ($M/1000$ to $M/5000$ acetic acid) and in varying dilu-
tions (1 unit in 50 to 500 cc.).
After elution and dialysis
Time-value = 0.2 to 0.16 minute

The final preparation of invertase gave no test for gum, a negative Millon test,
and a slight ninhydrin reaction, and contained 5 to 10 per cent of tryptophane.
In some cases, especially from yeast whose invertase content had been enriched
by feeding it sugar, the tryptophan content amounted to 2 to 3 per cent.

Schneider, in his chapter on carbohydrases in Oppenheimer
and Pincussen's *Methodik der Fermente*, page 849, states that
Willstätter and his coworkers were unable to obtain by adsorption
methods, invertase preparations having a time-value better than
0.2 to 1.5 minutes. They (122) succeeded, however, in some
instances, although not always, by adding diammonium phos-
phate to invertase solutions (time-value 0.2 minute) and then an
equivalent amount of lead acetate, in carrying down by the lead
phosphate formed material present in the solution to such an
extent as to reduce the time-value of the enzyme material still
remaining in the solution to 0.1 minute.

According to Lutz, working in the writer's laboratory (unpub-
lished work), preparations having time-values of about 0.2
minute and obtained by the Willstätter adsorption procedure,
are often mixtures of at least two invertase complexes differing in
their respective time-values or degree of activity. He finds that
a part of these highly active preparations obtained by the adsorp-
tion procedure is soluble in saturated ammonium sulfate, but not

[1] Fractional adsorption—using either less adsorbent than required for com-
plete adsorption, or incomplete elution.

all. The soluble part, after removal of the ammonium sulfate, has a time value of 0.1 minute, while the insoluble part is less active. Judging from Lutz's experience, it might be that the lead phosphate, in the Willstätter and Schneider experiments mentioned above, carried down the invertase complex insoluble in ammonium sulfate leaving the soluble part with the time-value of 0.1 minute remaining in the solution.

The compositions of the most active preparations obtained by Euler and Willstätter and their respective groups of coworkers varied quite widely, depending upon the procedure followed in preparing them. The ash contents ranged from 0.45 per cent (119) to 5.7 per cent (23). Willstätter, Grasser, and Kuhn (116) have been able to lower the phosphorus content to 0.006 per cent, indicating that it is not an essential component of the enzyme. Euler and Josephson found 1.4 per cent sulfur in the preparation whose ash content was 5.7 per cent, but some of their other highly active preparations contained less. Most of the very active preparations prepared in the Munich laboratory ran quite high in nitrogen, containing from 5 to 12 per cent (119).

Euler and Josephson (22) are inclined to look upon invertase as a complex compound, consisting of a soluble protein intimately associated with an active group. Although the latter constitutes the seat of the catalytic properties of the enzyme, still the protein part plays a significant rôle in the way it influences the specificity as well as the activity of the enzyme. Some of the evidence which they offer as support for their view is as follows: proportionality between the nitrogen content and the activity (21); the presence of tryptophan and sulfur in their preparations (22); the acid and base dissociation constants, K_a and K_b, suggesting an isoelectric point like that of most proteins (pH = 4.5 to 5); molecular weight of about 20,000 (by diffusion) (27); and the inactivation of invertase by proteolytic enzymes like trypsin (22).

Willstätter (107) regards the above evidence put forth by Euler and Josephson as not convincing. In his laboratory they claim to have prepared invertases, not only free from tryptophan but likewise practically free from phosphorus, on the presence of both of which Euler and Josephson place so much weight. Nei-

ther have Willstätter and his students found any parallelism between nitrogen content and activity, in fact, they claim to have obtained invertase preparations free from protein and others free from yeast gum. Their concept (121, 122) of yeast invertase is that it consists of a catalytically active group, of still unknown constitution, adsorbed or at least loosely bound to a colloidal carrier. The carrier need not always be the same substance, but several of the substances, such as proteins, peptides, gums, etc., which usually accompany the enzyme in its preparations may play this part. The colloidal carrier (116) does not determine how the enzyme acts catalytically and is therefore different from Euler's concept of the enzyme, but the destruction of the carrier leaves the otherwise active group inactive. From this point of view, Willstätter and his students interpret Euler and Josephson's inactivation of invertase by trypsin as due to the latter breaking down a protein carrier.

One of the classical methods for obtaining naturally occurring substances in the pure state is crystallization. This method also has been applied to enzymes, and the first crystallized enzyme was obtained by Sumner (97) when he succeeded in isolating from jack-bean meal a crystalline globulin having 730 times more activity than the purest preparation of urease obtained up to that time.

Since then Northrop (85) has crystallized pepsin in large quantities from solutions of commercial pepsin preparations, and lately, together with Kunitz (87), has also isolated trypsin in the crystalline state. Recently Caldwell, Booher, and Sherman (9) reported the crystallization of pancreatic amylase. So far, however, yeast invertase has not been obtained in the crystalline form.

The question naturally arises as to whether the crystalline enzyme preparations are the enzymes in the pure form. If they are, then, of course, these enzymes at least are proteins. Willstätter (109) who claims, as has been mentioned above, that enzymes are made up of a catalytically active group, usually associated with a protein as a carrier, points out that all the crystalline enzymes obtained so far were obtained by using methods for crystallizing proteins, and hence one would expect the crystals

to be protein.   Both Northrop and Sumner admit the possibility
of active groups being attached to their crystalline protein prepa-
rations, or of crystalline proteins having an active prosthetic
group, like the porphyrin group in hemoglobin.   But Northrop
emphasizes the point that if the enzyme consists of a protein
and an active group, then these two are held together chemically
and not by adsorption as claimed by Willstätter (108).   That
crystalline pepsin is a single chemical individual and not a mix-
ture, Northrop has shown by the fact that repeated crystalliza-
tion has no influence on the optical activity of the product or
on the composition or the degree of activity.   He has also ex-
amined the solubility of the crystalline enzyme in a series of
different salt solutions and in every case the material behaved as
a single compound.   As still further evidence for the protein
nature of pepsin, Northrop partly denatured the protein and
found the extent of denaturation and decrease in activity paral-
leled each other.   He also found that after allowing the denatured
protein to revert to its native state, according to the method of
Anson and Mirsky (2), the activity returned and the recovered
enzyme was indistinguishable from the original crystalline pepsin.

Waldschmidt-Leitz and Steigerwaldt (102) claim to have
hydrolyzed crystalline urease by means of trypsin, until the solu-
tion no longer gave a precipitate with sulfosalicylic acid, without
impairing the enzyme's activity.   Sumner (99), on the other
hand, finds that trypsin only attacks the protein in crystalline
urease after it has been denatured, and the enzyme is no longer
active.

Another point indicating enzymes to be proteins is the claim
made by several investigators that enzymes possess antigenic
properties.   Lüers and Albrecht (62) state that they have ob-
tained a serum from rabbits, previously injected with malt amy-
lase preparations, which exerted considerable retarding effect on
the activity of this enzyme.   Recently Sumner and Kirk (98)
have succeeded in preparing a serum which strongly inhibited
the action of urease.   Matsuoka (63) claims similar results in
the case of yeast invertase.

The various methods for isolating invertase from yeast, the

methods for securing highly active preparations, and the determination of the compositions of these active preparations, thus far described, may be looked upon as a more or less direct approach to the unravelling of the chemical nature of the enzyme. In contrast to this direct method of attack, a sort of indirect one based on the kinetics of the hydrolysis reaction has also received considerable attention. Conditions such as the pH of the solution in which the enzyme is acting, the concentrations of sucrose and invert sugar, and the presence of other substances, all have a bearing on the magnitude of the activity of the enzyme.

Sörensen (95) was among the first to examine, in a quantitative way, the relation between the activity of invertase and the pH of the solution. Unfortunately his experiments were carried on at such a high temperature (52.5°C.) that the results obtained may possibly have been influenced by some destruction of the enzyme. Since then Michaelis and Davidsohn (69) have repeated Sörensen's experiments, but at room temperature. The relationship which they found to exist between activity and pH is illustrated graphically in figure 1. The curve shows that the enzyme manifests a maximum activity at about pH = 4.5 and that the velocity of hydrolysis decreases both on the more acid and more alkaline sides of this optimum pH. The portion of the curve on the more alkaline side, pH = 4.5 to 8, resembles the shape of the ionization curve of a weak acid, having as its ordinates the fraction of the acid remaining unionized or $(1 - \alpha)$, and as abscissae the pH of the solution. This, as Michaelis and Davidsohn point out, suggests that within this pH range invertase behaves as though it were a weak acid ionizing as

Invertase acid $\rightleftarrows$ invertase anion and H^+

and that only the unionized invertase is capable of catalyzing the hydrolysis of sucrose. Similarly, the portion of the curve corresponding to the more acid range, pH = 2 to 4.5, resembles the ionization curve of a weak base and has led Michaelis and Davidsohn to claim that invertase is amphoteric.

This amphoteric behavior is very much in line with the claim that invertase is a protein with an isoelectric point in the neigh-

borhood of pH = 4.5, the isoelectric point common to many proteins. Too much weight, however, must not be attached to the shape of the more acid branch of the curve in figure 1, because invertase is very easily inactivated when the acidity of the hydrolyzing sucrose solution is greater than pH = 4.0. This makes the experimental error in this region considerable (75), and it

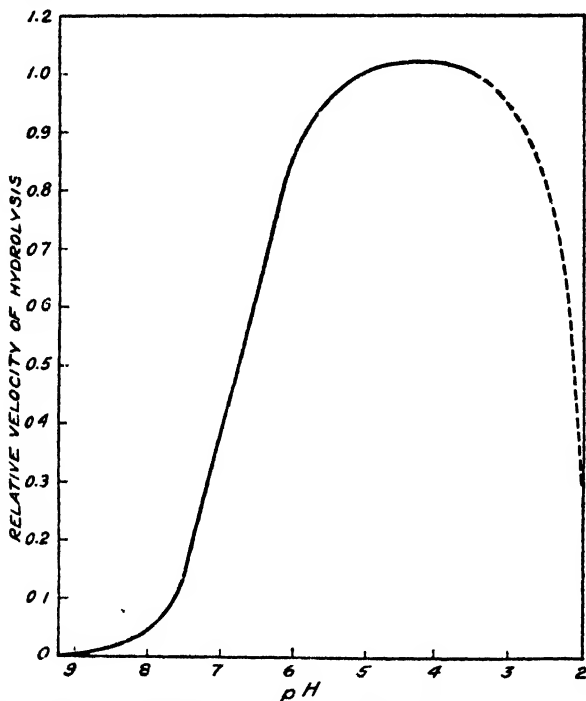FIG. 1. RELATIONSHIP BETWEEN THE pII AND ACTIVITY OF A YEAST INVERTASE PREPARATION

Michaelis and Davidsohn: Biochem. Z. **35**, 405 (1911)

will be observed that Michaelis and Davidsohn represented the acid branch of the curve by a dotted line.

There was a great deal of speculation by the earlier investigators as to the way in which invertase acted on the sucrose molecule. In 1902 Adrian Brown (8) hydrolyzed, using a constant amount of enzyme in equal volumes, a series of sucrose solutions, ranging in concentration from 5 to 40 per cent, and

found that the amount of sugar inverted per unit time was practically constant, irrespective of the sucrose concentration. This constancy in the quantity of sucrose hydrolyzed led him to formulate the hypothesis that the invertase combines with sucrose according to the simple mass-law principle, i.e., molecule for molecule, to form an invertase–sucrose compound, and that the velocity of hydrolysis is proportional to the concentration of the compound.

Since then, Michaelis and Menten (68) and others (73) have found that in the case of sucrose solutions below 5 per cent the velocity increases gradually as the sugar concentration is increased, and reaches a maximum value when the concentration is about 5 per cent. Looking at this gradual increase in the rate of hydrolysis from the standpoint of Brown's hypothesis, it appears that the equilibrium point of the reaction

$$\text{Sucrose} + \text{invertase} \rightleftarrows \text{sucrose–invertase compound} \qquad (1)$$
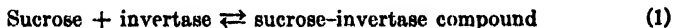
is such that below 5 per cent sucrose part of the invertase is present in the solution in the free condition. It is, of course, impossible to determine directly the relative amounts of the enzyme present in the solution as combined and free enzyme. Therefore, instead of trying to test experimentally the mass-law expression,

$$\frac{\varphi}{\phi} = \frac{S}{S + K_s} \qquad (2)$$

in which φ and ϕ represent respectively the combined and total invertase concentrations,[2] S the concentration of free sucrose, and K_s the equilibrium constant, Michaelis and Menten had the clever idea of using relative initial velocities as the measure of the first term in equation 2.

$$\text{Relative initial velocity} = \frac{S}{S + K_s} \qquad (3)$$

[2] The term $\dfrac{\varphi}{\phi}$ in equation 2 represents the fraction of the enzyme combined with sucrose. Since the velocity of hydrolysis is proportional to the concentration of the combined enzyme, it follows that the maximum velocity occurs when $\dfrac{\varphi}{\phi} = 1$. Therefore, putting the velocities corresponding to a series of dilute solutions, all

Figure 2 contains a comparison of the Michaelis and Menten velocity measurements (o) with the theoretical mass-law curve (full-line curve), derived by substituting different values for S in the second member of equation 2 and using the proper value for the equilibrium constant K_s. The agreement between experiment and theory is quite satisfactory.
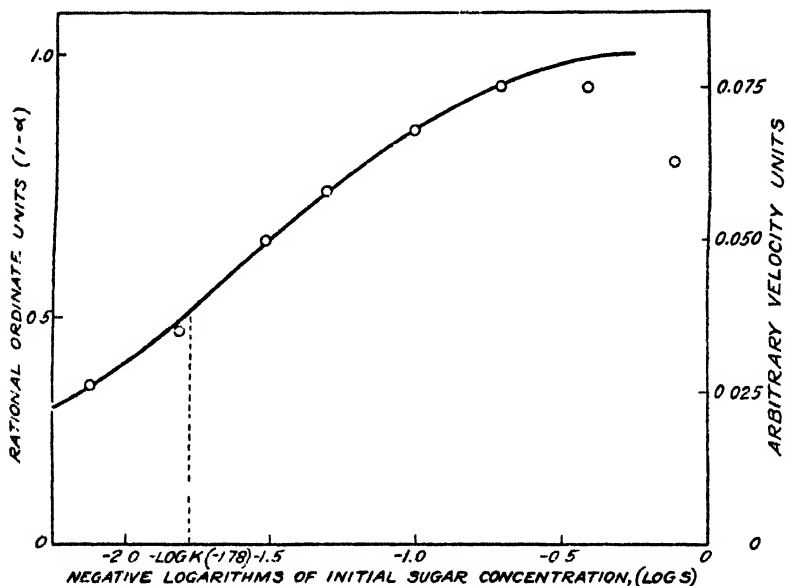

Fig. 2. Comparison of the Mass-law Curve with the Change in Activity of Yeast Invertase as the Concentration of Sucrose is Varied

Michaelis and Menten: Biochem. Z. **49**, 333 (1913)

Two other points arising from Michaelis and Menten's work also should be mentioned. It is evident that when the first term

containing the same concentration of enzyme but varying concentrations of sucrose, on a relative basis with the maximum velocity equal to 1, then these relative velocity values can be substituted for the term $\frac{\varphi}{\phi}$ in equation 2. Initial velocities were used because at the beginning of the reaction, practically no sucrose has been hydrolyzed. This, coupled with the assumption that the concentration of invertase is negligible compared to that of sucrose, makes it possible to use the original concentration of sucrose to represent S, the concentration of uncombined

in equation 3 is equal to 1/2, then S equals K_s. This means that the concentration of sucrose corresponding to half the maximum velocity of hydrolysis is numerically equal to the dissociation constant of the sucrose–invertase compound. In other words, here is a method for determining the affinity of the enzyme for sucrose. The second point relates to retardation. The presence of any foreign material in the hydrolyzing sucrose solution is apt to affect the activity of invertase. Even the invert sugar formed during the course of the hydrolysis slows up the velocity and hence makes the kinetics of this type of inversion different from that brought about by mineral acids. Michaelis and Menten also examined the relationship between the extent of retardation caused by fructose and glucose and the concentration of the retardant and reached the conclusion that these sugars retard by also combining with the invertase, thereby leaving less of the latter free to unite with the sucrose.

All retardants, however, do not affect the enzyme's activity in the way glucose and fructose do. Thus Michaelis and Pechstein (70) claim that substances such as ethyl alcohol and α-methylglucoside affect the rate at which the sucrose–invertase compound breaks down into invert sugar and free enzyme. In other words, the action of invertase can be retarded in either of two ways,— the retardant may compete with sucrose for the enzyme, as for example glucose and fructose do, or it may affect the medium in such a way that the sucrose-invertase compound breaks down more slowly, as alcohol and α-methylglucoside do. Haldane (37) has suggested the descriptive names, "competitive" and "noncompetitive," for these two types.

Michaelis' publications on the kinetics of invertase action served as a great stimulus for further researches along these lines. Euler (24), commenting on Michaelis' work, states: "Michaelis, as is well known, was the first to determine the affinity constant of an enzyme for its substrate as well as for its cleavage products, and on the basis of these measurements he has developed a theory for the kinetics of enzyme action which, together with certain modifications, constitutes one of the fundamental principles upon which scientific enzyme studies rest."

Among the first to apply the Michaelis-Menten method for determining the affinity of an invertase preparation for sucrose were Euler and Laurin (20). The interesting outcome of their measurements was the fact that their enzyme preparation, from a Swedish brewery yeast, gave a higher value, K_s = 0.025, instead of 0.0167 as reported by Michaelis and Menten. Shortly afterwards, Kuhn (52), working in Willstätter's laboratory, measured the dissociation constants, K_s, for a series of invertase preparations. Some of these preparations were obtained from the same yeast, but differed from each other in the degree of purification to which they had been subjected. Other preparations were prepared from different strains of yeast. Some of Kuhn's values

TABLE 1

Values of K_s for a series of invertase preparations

ENZYME PREPARATION	DEGREE OF PURITY TIME-VALUES	K_s
	minutes	
Distillery yeast, Race 12...	Very crude	0 016
American brewery yeast	6 3	0 020
Lion Brewery yeast...	180 0	0.029
Highly purified preparation from Lion Brewery yeast.	0 85	0.029
Preparation from another Lion Brewery yeast.. .	0.20	0.040

are given in table 1, and it will be noted that purification appears to have no effect on the value of the constant. On the other hand, the values for K_s for preparations from different yeasts varied among themselves quite widely.

The fact that the degree of purification seems to be without influence on the value of the dissociation constant, Kuhn points out, constitutes further support for Willstätter's claim that the invertase particle consists of a colloidal carrier to which a catalytically active group is attached, and that the colloidal condition of the carrier, its composition, etc., have no influence on the catalytic properties of the active group. He also points out that for analytical purposes, such as the quantitative estimation of invertase units, etc., which depend on velocity measurements,

the value of the dissociation constant is an important factor, because the size of the constant determines the concentration of the sucrose–invertase compound upon which the velocity of hydrolysis depends. For this reason Willstätter and Kuhn (114) recommend that the value of the dissociation constant of the sucrose–invertase compound be included in the description of invertase preparations.

The Michaelis method for determining the dissociation constant, K_s, or its reciprocal, the affinity constant, has been widely used by the European chemists, especially Euler and Willstätter and their respective collaborators, as a guide in their studies of specificity and the classification of enzymes. The experiences of the present writer and his coworkers, however, have made them hesitate in adopting the method in such a whole-hearted way. In the first place, Michaelis and Rothstein (71) found that the two relationships, the pH-activity curve of Michaelis and Davidson (figure 1) and the ps-activity[3] curve of Michaelis and Menten (figure 2) can not be reconciled. Expressing (69) the two relationships, by letting ψ, ϕ, ϕ^- and φ represent total, unionized, ionized, and combined invertase, respectively, and S the concentration of uncombined sucrose, then

$$\frac{\phi^- \cdot H^+}{\phi} = K_H, \quad \frac{\phi \cdot S}{\varphi} = K_s, \quad \text{and } \psi = \phi + \phi^- + \varphi$$

and

$$\text{Relative initial velocity} = \frac{\varphi}{\psi} = \frac{1}{1 + \frac{K_s}{S} + \frac{K_s K_H}{SH}} \tag{4}$$

According to equation 4, if the Michaelis-Davidsohn pH-activity curve were determined at several different concentrations of sucrose, a family of curves should result, distributed along the pH axis in figure 1. Michaelis and Rothstein found this not to

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[3] In the case of the curve in figure 2, the negative logarithm of the sucrose concentration is plotted against velocity, just as in the case of the pH-activity curve in figure 1 the negative logarithm of the hydrogen-ion concentration is plotted against the velocity. And just as the latter is often termed the pH-activity curve, so the former is often called the ps-activity curve.

be the case, but instead the same curve resulted, irrespective of the sucrose concentration employed. This obviously means that the pH-activity curve is independent of the sucrose concentration. Similarly, looking at Michaelis and Rothstein's results from the standpoint of the pH-activity curve, the latter turns out to be independent of the hydrogen-ion concentration. On the strength of Michaelis and Rothstein's work, Kuhn (52) suggests that the pH of the hydrolyzing sucrose solution has nothing to do with the reaction involved in the union of the sucrose and invertase, but that it influences the rate at which the sucrose–invertase compound breaks down into invert sugar and enzyme.

Contrary to the findings of Michaelis and Rothstein, A. H. Palmer in this laboratory (unpublished observations) finds that the ps-activity curve (figure 2) is influenced by pH, especially when different buffers are employed to regulate the pH of the hydrolyzing sucrose solutions. For example, the curve resulting when sodium citrate is the buffer has a different slope from the curve resulting, at the same pH, when sodium phosphate is used. Larson (59, 79), using citrates and phosphates and a series of sucrose solutions of different pH values, was unable, in many instances, to find any close agreement between the experimental and theoretical ps-activity curves.

If the reader will look at the ps-activity curves in figure 2, he will notice that the velocity of hydrolysis commences to decrease when the concentration of sucrose exceeds 5 per cent (log S = -0.84). Other curves of the same kind in the Michaelis and Menten paper (68) show even greater deviation from the theoretical (full-line curve in figure 2) than the one shown in figure 2. Michaelis (66) suggests that this discrepancy between the experimental data and the theory may be due to the mass-law no longer holding rigidly in the more concentrated sugar solutions. It must be borne in mind, however, that water is also a reactant in the hydrolysis of sucrose, and the Brown-Michaelis theory does not take it into account. Curve 1 in figure 3 shows the change in the velocity of hydrolysis of sucrose by yeast invertase as the concentration of sucrose is increased up to 70 per cent. Its shape suggests that between 5 and 70 per cent sucrose the velocity is

some simple function of the sugar concentration. But as Ingersoll (43, 44) has pointed out, the concentration of water also drops off linearly with the increase in sucrose concentration, and when the velocity is plotted against the concentration of water, curve 1 in figure 4 results. Since these two curves are so similar in shape, Ingersoll was unable to decide whether it is the concentration of sucrose or that of water which determines the magnitude of the velocity of hydrolysis. Nelson and Schubert (81), however, found it possible to vary the concentrations of water and sucrose independently of each other by adding given quantities of alcohol to the hydrolyzing sucrose solutions. Their results are shown graphically by means of curves 2 and 3 in figures 3 and 4. As has already been stated, the curves marked 1 in figures 3 and 4 represent the velocities corresponding to different concentrations of sucrose and water respectively, while curves 2 and 3 represent the velocities when part of the sucrose has been replaced by alcohol. It will be noticed that when the velocities are plotted against water concentration, then the curves 2 and 3 in figure 4 lie very close to curve 1 for sucrose alone; on the other hand, when the velocities are plotted against the sucrose concentration, curves 2 and 3 in figure 3, then they are spread farther apart. Since the alcohol curves, 2 and 3 in figure 4, fall so close to curve 1, for sucrose alone, it becomes evident that the velocities are nearly the same, irrespective of the particular amount of alcohol and sucrose which the solution contains, provided that the concentration of water is the same. In other words, the concentration of water is a primary factor in determining the magnitude of the velocity of hydrolysis when the concentration of sucrose is large, and the concentration of sucrose is only of minor significance.

Since the concentration of water exerts such a dominating influence on the velocity in the case of solutions containing more than 5 per cent of sucrose, it would not be surprising to find this influence to extend to solutions containing less than 5 per cent of sucrose, but gradually diminishing as the sugar solutions became more and more dilute. If there is an influence due to the water concentration in the region below 5 per cent of sucrose, then obviously the Brown hypothesis does not describe the reaction be-
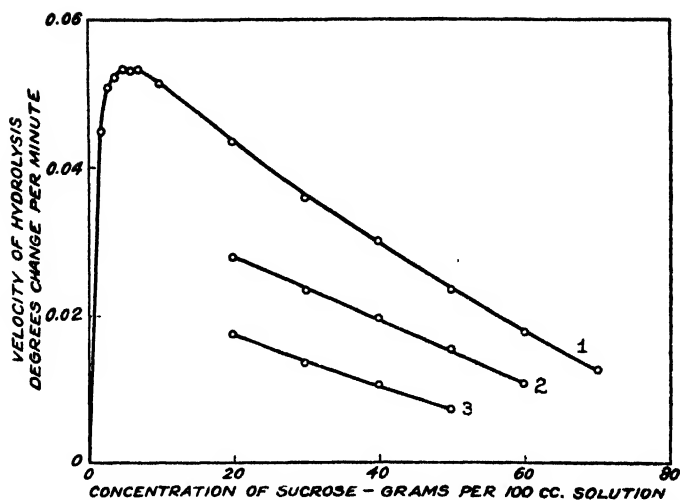
FIG. 3. CHANGE IN THE RATE OF HYDROLYSIS WITH CHANGE IN CONCENTRATION
OF SUCROSE, IN THE ABSENCE AND IN THE PRESENCE OF 10 AND 20 PER
CENT ETHYL ALCOHOL

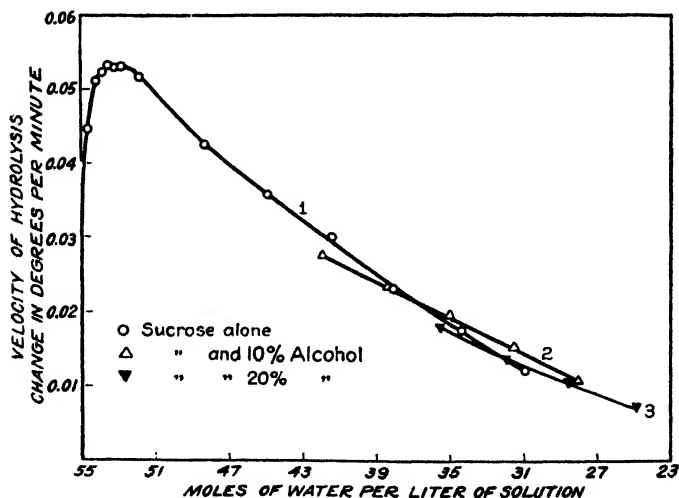Nelson and Schubert: J. Am. Chem. Soc. **50**, 2188 (1928)

FIG. 4. THE SAME DATA AS REPRESENTED IN FIGURE 3, EXCEPT THAT THE
RATE OF HYDROLYSIS HAS BEEN PLOTTED AGAINST WATER CONCENTRATION

Nelson and Schubert: J. Am. Chem. Soc. **50**, 2188 (1928)

tween the enzyme and sucrose, and the Michaelis-Menten disso-
ciation constant loses its significance.

It is quite generally recognized that invertase, up to the present
at least, must be regarded as colloidal, and hence strictly speaking,
its reaction with sucrose must be heterogeneous rather than
homogeneous, as assumed in the Brown-Michaelis theory. Bay-
liss (5), in his *Nature of Enzyme Action*, not only favored the view
that the reaction of an enzyme like invertase belongs to the hetero-
geneous class, but he also argued that water is an important
reactant in the hydrolysis of the substrate, and hence the rôle
which it plays should also be taken into account in the formula-
tion of any hypothesis as to the chemical mechanism of the reac-
tion. "We may suppose that in the hydrolysis, for example, the
substrate is brought into intimate relation with water on the
surface of the particles of the enzyme. . . . . It must be under-
stood that adsorption is merely a preliminary state, and that after
it has taken place, the proper chemical reaction makes its ap-
pearance."

The idea that water as well as sucrose combines with the
enzyme makes it possible to account for the fact that the velocity
of hydrolysis increases as the concentration of sucrose increases
up to 5 per cent and then decreases as the concentration of the
sugar is increased still more, in a way different from that advo-
cated by Michaelis. The reaction might be heterogeneous and
the velocity dependent on the relative amounts of sugar and
water on the surface of the enzyme particles. This idea is in
line with Freundlich's idea of this type of a reaction. He (34)
states: "In this group of processes the velocity will certainly
depend upon the concentrations of the two adsorbed materials
at the boundary surface. Now since one substance displaces the
other, we have the important conclusion that the velocity, as it
varies with the concentration (or amount adsorbed as the case
may be) of each of the two substances, passes through a
maximum."

Michaelis and Menten failed to take into account whether the
different mutameric forms of glucose and fructose retard yeast
invertase action to the same extent. When Willstätter and

Kuhn (112, 113, 53) compared these different forms in this respect they found that they were quite different in their inhibiting influences. They also found that invertases prepared from material other than yeast were retarded differently by these mutamers. An invertase preparation from a Munich brewery yeast was not retarded at all by α-glucose, but was by the β-mutamer and by mutarotated fructose. On the other hand, an invertase from *Aspergillus oryzae* (taka-diastase) showed quite the opposite effect (54).

	Yeast Invertase	*Taka-invertase*
α-Glucose..........	No retardation	Retarded
β-Glucose...........................	Retarded	No retardation
$\alpha\beta$-Fructose........................	Retarded	No retardation

These differences in the retardation of the activities of the invertases have been interpreted by Willstätter and Kuhn to mean that yeast invertase possesses no affinity for the α-glucose, and that taka-invertase can not combine with fructose but only with α-glucose. Furthermore, when an invertase combines with sucrose to form the sucrose–invertase compound, it does not attach itself to the sucrose molecule as a whole, but either to the glucose or the fructose end of the disaccharide molecule, depending on whether, as they have termed it, it is a *gluco-* or a *fructo-* invertase. Yeast invertase, which is retarded by fructose, is a fructo-invertase and attaches itself to the fructose part of sucrose, while taka-invertase is a gluco-invertase and forms the sucrose-invertase compound by attaching itself to the glucose end.

As further support for this classification of invertases, Kuhn (55, 56) points out that all the higher saccharides such as the following,

Sucrose......................................	Glucose <> fructose
Gentianose.........................	Glucose < glucose <> fructose
Raffinose........	Galactose < glucose <> fructose
Stachyose .... Galactose < galactose	< glucose <> fructose
Hesperonal................. Phosphoric acid	< glucose <> fructose

which not only have sucrose as a component but in which the fructose is present in the molecule in the same condition as in sucrose itself, are hydrolyzed by yeast invertase. On the other

hand, they found these modified sucrose sugars to be unaffected by taka-invertase. This they argued, is to be expected, because in each case the glucose end of the sucrose molecule has been modified by having attached to it some other group, such as a second glucose, a galactose, etc., leaving thereby no α-glucosidic group for a gluco-invertase, like taka-invertase, to combine with. They also point out (57) that the trisaccharide, melezitose (glucose < > fructose > glucose) is hydrolyzed by three different gluco-invertases, taka-invertase, and invertase preparations from *Aspergillus niger*, and from *Penicillium glaucum*, but not by yeast invertase, because in this case the fructoside group necessary for a fructo-invertase is absent.

Euler and Josephson (24) found, contrary to the German investigators, that an invertase preparation from a Swedish brewery yeast was retarded by α-glucose, as well as by β-glucose and αβ-fructose. This has led Kuhn and Münch (55) to repeat their experiments, using this time not only a sample of the Swedish enzyme preparation but also preparations from several other yeasts. Not only did their results turn out to agree with those of the Stockholm chemists, as far as the Swedish invertase preparation was concerned, but they also found that several of the other invertases were retarded by α-glucose. But by applying the Michaelis criteria[4] for deciding the kind of retardation, Kuhn

[4] Putting ϕ, φ and ψ to represent respectively the concentrations of total invertase, invertase combined with sucrose, and invertase combined with retardant, and S and R the concentrations of free sucrose and free retardant, then for a competitive retardant

$$S (\phi - \varphi - \psi) = K_S \varphi$$
$$R (\phi - \varphi - \psi) = K_R \psi$$

or

$$\frac{K_R}{K_S} = \frac{R}{S \left(\dfrac{\phi}{\varphi} - 1 \right) - K_S} \tag{5}$$

Since the velocity of hydrolysis is assumed to be proportional to the concentration of the sucrose-invertase complex, if φ_0 represents the concentration of the complex in the absence, and φ the concentration in the presence of the retardant, and v_0 and V the respective velocities, then

$$\varphi_0 : \varphi = v_0 : V \tag{6}$$

and Münch (56) claim that the retardations by α-glucose, for all of the yeast invertase preparations affected by the hexose, were non-competitive in character and therefore different from the retardations by fructose, all of which were found to be competitive.

Nelson and Anderson (1, 78) also studied the retardation of yeast invertase action by the mutameric forms of glucose and fructose. In order to retain the hexoses in their original mutameric form as much as possible during the course of the hydrolysis, they conducted the hydrolysis at practically zero degrees.

Upon inspection of figure 5, it can be seen that the retardation of α-glucose is different from the others, and therefore, in this respect, agrees with the observations of Kuhn and Münch. But the experimental data, in the case of α-glucose, contrary to those of Kuhn and Münch, did not conform to the requirement for a non-competitive retardant, nor did the data for β-glucose and β- and αβ-fructose conform to the specifications for a competitive retardant (1). In other words, these results did not fall in line with the gluco-fructo-invertase theory.

Another interesting case of the influence of β-glucose on the activity of an invertase has been observed by Nelson and Sottery (80). The invertase occurring in honey does not hydrolyze raffinose, is only slightly retarded by α-methylglucoside, and hence in these two respects resembles taka-invertase (38). Instead of not being retarded by β-glucose, as Kuhn had observed in the case of taka-invertase, it actually, when present in small con-

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and, in the absence of the retardant

$$\frac{v_0}{\phi} = \frac{\omega}{S + K_S} \tag{7}$$

(see equation 3)

By means of equations 6 and 7, equation 5 may be written

$$\frac{K_R}{K_S} = \frac{R}{\left(S + K_S\right)\left(\dfrac{v_0}{V} - 1\right)} \tag{8}$$

Retardation due to a competitive retardant will conform to equation 8, while retardation due to a non-competitive retardant, which only affects the rate of decomposition of the sucrose–invertase complex, gives constant values for $\frac{v_0}{V}$, irrespective of the concentration of the sucrose.

centrations, exerts an accelerating effect (see figure 6). This effect, however, depends not only on the concentration of the β-glucose but also on the concentration of the sucrose. When this hexose is present in higher concentrations, then it acts as a retardant.

A long series of papers by Euler and Josephson on the affinity of yeast invertase for different sugars has appeared during the past six years, mostly in the Zeitschrift für physiologische Chemie.
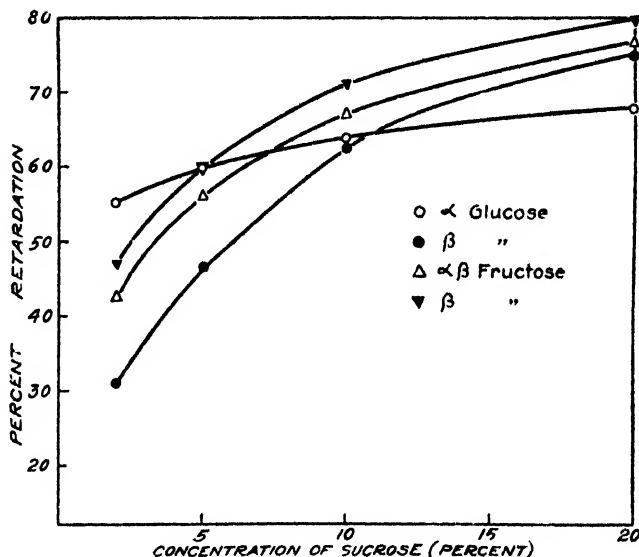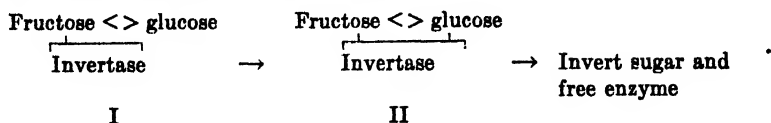

FIG. 5. PER CENT RETARDATION CAUSED BY 8 PER CENT GLUCOSE OR FRUCTOSE AT DIFFERENT CONCENTRATIONS OF SUCROSE

Nelson and Anderson: J. Biol. Chem. 69, 443 (1926)

These investigators have proposed another theory known as the two affinities theory (14, 15, 25, 26), which, like the Willstätter and Kuhn theory, is based upon the Michaelis method for determining the affinity of an enzyme for its substrate. In this theory, they argue that invertase has two kinds of affinities, distinctly different in character. The one, which they have designated as primary, is strictly specific (in the case of yeast invertase) to fructose alone; while the other, a secondary sort of affinity, can

combine not only with glucose but with many other substances. Their idea may be represented as

Fructose <> glucose   Fructose <> glucose

Invertase   →   Invertase   →   Invert sugar and
                                                              free enzyme

I   II

in which the part played by the primary affinity is shown by I and that by the secondary by II.   Compound I is formed at first and then gradually goes over to II.   The latter is unstable,
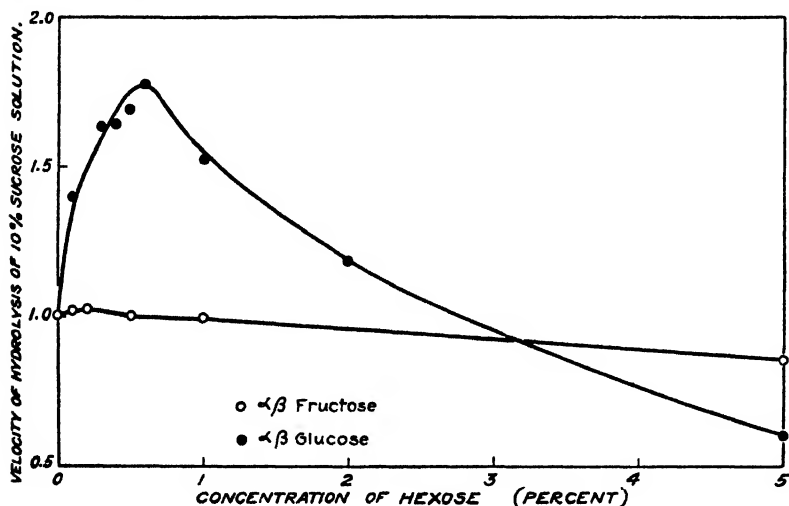
FIG. 6. INFLUENCE OF DIFFERENT CONCENTRATIONS OF GLUCOSE AND FRUCTOSE
ON THE ACTIVITY OF HONEY INVERTASE

Nelson and Sottery: J. Biol. Chem. 62, 139 (1924)

breaking down rapidly to invert sugar and free invertase, thereby causing the concentration of II to be small and the change from I to II irreversible.   When a retarding substance, such as glucose, α-methylglucoside, or ethyl alcohol, is added to the hydrolyzing sucrose solution, it can unite with the less specific secondary affinity and thereby hinder the formation of the intermediate compound, II, upon the concentration of which the rate of hydrolysis of the sucrose depends (26).   If a substance other than

glucose, in the form in which it occurs in the sucrose molecule, happens to be attached to the secondary affinity, it may influence the magnitude even of the primary affinity in such a way as to lower the concentration of I or the rate at which I goes over to II, and in this way exert a retarding influence (25).

The Kuhn theory that there are two types of invertase, based chiefly upon the fact that his taka-invertase preparations fail to hydrolyze raffinose and that this enzyme is retarded by α-glucose, has been threatened by several recent observations. One of the first of these observations occurred in Kuhn's own laboratory, when Miss Rohdewald (56) incidentally encountered a taka-invertase preparation which did hydrolyze raffinose. This was followed by Schlubach and Rauchalles (92) succeeding in hydrolyzing, by means of taka-invertase preparations, both the α- and β- forms of h-methylfructoside. Leibowitz and Mechlinski (60), repeating the Rohdewald experiment, reached the conclusion that taka-invertase preparations sometimes contained melibiase, and that the hydrolysis of the raffinose was due to the latter enzyme breaking down the trisaccharide into galactose and sucrose, and the sucrose, thus set free, then being hydrolyzed by the taka-invertase. Their explanation, however, appears to be incorrect, because Weidenhagen (104) since then has succeeded in hydrolyzing raffinose by a taka-invertase preparation which was free of melibiase. Besides showing that taka-invertase, contrary to Kuhn and Willstätter, does hydrolyze raffinose, Weidenhagen (104) has demonstrated that one of his preparations was twice as efficient as yeast invertase in catalyzing the hydrolysis of raffinose. Similarly, the classification of invertases on the basis of whether their activity is retarded by α-glucose or fructose has become doubtful. For example, Weidenhagen (104) has shown that the invertase from *Penicillium glaucum,* which Euler, Josephson, and Söderling (28) classified on the basis of retardation experiments as a gluco-invertase, hydrolyzes raffinose and hence can not be so classified. But one of the most interesting observations made by Weidenhagen (103) is the hydrolysis of sucrose by maltase, which has always been regarded as inactive towards this sugar. The reason why this has not been observed earlier is that

the pH-optimum of yeast maltase is in the neighborhood of 7, and most sucrose hydrolyses have been run in the pH range 3 to 6, the range most suitable for yeast invertase.
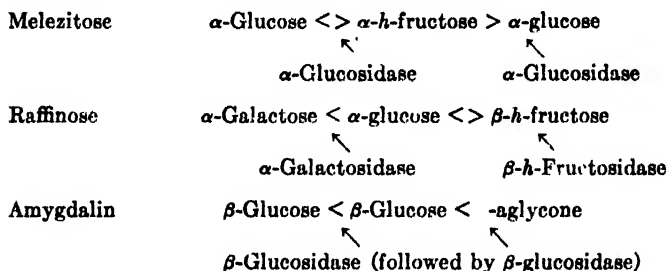
On the strength of observations like those mentioned above, Weidenhagen (103) claims that Kuhn's classification of the invertases into two groups, gluco- and fructo- invertases, depending on their retardation by glucose and fructose, is not justified. The carbohydrases should be classified according to the particular type of glycoside which they hydrolyse. α-n-Glucosides are hydrolyzed by α-n-glucosidase and β-galactosides, like lactose, are hydrolyzed by β-galactosidase, etc.

α-Glucosidase...... α-Methylglucoside, maltose, sucrose, melezitose
β-Glucosidase...... β-Methylglucoside, gentiobiose, cellobiose
α-Galactosidase.... α-Galactosides, melibiose, raffinose
β-Galactosidase.... β-Galactosides, lactose
β-h-Fructosidase... β-h-Methylfructoside, sucrose, raffinose, gentianose

According to Weidenhagen, yeast and taka-invertase preparations consist chiefly of β-h-fructosidase; maltase preparations, whether prepared from yeast or malt extract are mainly α-n-glucosidase; while emulsin contains β-n-glucosidase, etc. Frequently preparations like these are mixtures of glycosidases. Crude yeast invertases contain often considerable α-n-glucosidase mixed with the β-h-fructosidase. Some taka-invertase preparations hydrolyze melezitose, owing to the presence of α-n-glucosidase.

Sugars which differ by means of the asymmetry of their glycosidic carbon atoms, like α- and β-n-methylglucosidases, or sugars which differ by the asymmetry of other carbon atoms, like α-n-methylglucoside and α-n-methylgalactoside, require specific enzymes. γ-Glycosides require different enzymes from those active towards normal glycosides. Thus β-h-fructosidase (yeast invertase) hydrolyzes β-h-methylfructoside but not β-n-methylfructoside (58, 33, 42), and α-n-glucosidase (yeast maltase) hydrolyses α-n-methylglucoside but not α-h-methylglucoside. The specificity of a glycosidase is also dependent on the length of the carbon chain in a sugar. Neither α-n-glucosidase (yeast maltase) nor β-n-glucosidase (emulsin) affect the α- or β-n-methylxylosides, etc. (32, 47).

Weidenhagen (103) holds that there are no enzymes specific to particular disaccharides, like sucrose, maltose, etc. These sugars, being glycosides, are acted upon by their respective glycosidases. Thus, sucrose is hydrolyzed by α-n-glucosidase because it is an α-n-glucoside and by β-h-fructosidase because it is also a β-h-fructoside, while maltose, being only an α-n-glucoside, is only attacked by α-n-glucosidase. The same holds for trisaccharides.

Melezitose	α-Glucose <> α-h-fructose > α-glucose
	α-Glucosidase α-Glucosidase
Raffinose	α-Galactose < α-glucose <> β-h-fructose
	α-Galactosidase β-h-Fructosidase
Amygdalin	β-Glucose < β-Glucose < -aglycone
	β-Glucosidase (followed by β-glucosidase)

Weidenhagen's ideas concerning the specificity of the carbohydrases has attracted considerable interest among the workers in this field, but it is too early to predict how generally they will be adopted. Already several have come forward with cases which seem to be difficult to reconcile with the theory. Karström (48) mentions an enzyme preparation from *Bacterium coli* which hydrolyzes maltose, but which he found to be without action on sucrose. According to Weidenhagen, any enzyme which hydrolyzes maltose must also hydrolyze sucrose, because hydrolyzing maltose classifies the enzyme as α-n-glucosidase, and sucrose being an α-n-glucoside should be hydrolyzed by it. Weidenhagen (103) has repeated Karström's experiments, and states that Karström's claim is incorrect, because the enzyme does hydrolyze sucrose. On the other hand, Myrbäck (72), also repeating Karström's experiments, reaches the same conclusions as Karström. Leibowitz (60) has been unable to hydrolyze α-methylglucoside by maltase obtained from malt, and Weidenhagen (103), on the basis of his own work, claims that Leibowitz used too weak a solution of the enzyme. Since then Pringsheim, Borchardt, and Loew (89) report that their maltase preparation, from malt extract, is

inactive towards α-methylglucoside. They also find that other maltases, prepared from *Aspergillus Wentii* and from *Aspergillus oryzae* (taka-diastase) are without action on α-methylglucoside. Ivanoff, Dodonowa, and Tschastuchin (45) find a maltase in mushrooms which hydrolyzes maltose but not sucrose. Mrs. Schubert, working in the writer's laboratory, has found that an invertase preparation from honey hydrolyzes maltose but seems to be without action on α-methylglucoside. Recently Willstätter (109) announced that Grassmann, working in his laboratory, has obtained experimental data which "corrects the views of Weidenhagen concerning their (carbohydrases) specificity."

Another question which has received considerable attention from workers studying carbohydrases by means of kinetics, is whether an enzyme is specific to one particular substrate, or whether it can hydrolyze several different substrates that are closely related steieochemically. For example, are all β-n-glucosides hydrolyzed by the same β-glucosidase, or are yeast invertase and yeast raffinase the same enzyme? According to Weidenhagen's theory, discussed above, they are the same. But certain observations have been encountered which make it difficult to dispose of the question in such a confident manner as Weidenhagen does. Raffinase, as is well known, may be looked upon as α-galactose attached to the glucose part of the sucrose molecule. Melibiase-free yeast invertase preparations, which according to Weidenhagen contain β-h-fructosidase, hydrolyze the β-h-fructosido linkages in both of these sugars. Willstätter and Kuhn (111) found, upon comparing the rates of hydrolysis of these two sugars by invertase preparations from a series of different yeasts, all *Saccharomyces cerevisiae*, that the ratios of these two rates varied. For example, the invertase in one preparation hydrolyzed sucrose 12.3 times faster than it did raffinose, while another preparation of the enzyme hydrolyzed sucrose only 5 times faster. At first Willstätter and Kuhn were inclined to look upon this variation in the ratio of the two rates as evidence for the presence of two distinctly different enzymes, the relative concentrations of which varied in the enzyme preparations obtained from the different lots of yeast. Against this idea of two distinct enzymes, however,

was their inability to alter the ratio of the two rates for any one preparation by further purification. If the enzymes are not identical, then a more or less fractional separation ought to occur upon further purification. Since then, Kuhn (52) has tried to find a satisfactory answer to this question in a different way. In determining the dissociation constant K_s, for the invertase-sucrose compound, by the Michaelis-Menten method (illustrated in figure 2), he found that this value varied with different invertase preparations. This would mean that different invertase preparations possess different tendencies to combine with sucrose. In determining the affinity values of different preparations for raffinose by determinations which seem to draw upon the imagination to some extent, Kuhn finds that these also vary. But the dissociation constants for the sucrose-invertase compounds do not necessarily parallel the corresponding dissociation constants of the enzyme-raffinose compounds. Thus, for example, two preparations of invertase may have the same affinity for sucrose, while their affinities for raffinose might vary from each other quite widely. This variation in the affinity constants would naturally give rise to variations in the respective concentrations of enzyme-substrate compounds upon which the rate of hydrolysis is supposed to depend. By correcting the velocity values so as to correspond to these variations in affinity, Kuhn finds that the ratio of the rates of hydrolysis of the two sugars remains constant, irrespective of the particular invertase preparation used, and therefore claims that yeast invertase and yeast raffinase are identical.

Josephson (46), working in Euler's laboratory, advances another argument for claiming these two enzymes to be the same. This proof, like that of Kuhn's, rests on the Michaelis-Menten method for determining the affinity constants of the substrate-enzyme and the retardant-enzyme compounds (see equation 5). He finds that both yeast invertase and yeast raffinase have the same affinity for competitive retardants like glucose and fructose, thereby demonstrating that in this respect the two enzymes behave alike.

Workers in the writer's laboratory have met with a peculiar behavior of yeast invertase, which possibly may be related to the

variation in the ratio of the rates of hydrolysis of sucrose and raffinose observed by Willstätter and Kuhn. Nelson and Papadakis (82) found on partially inactivating yeast invertase, free from melibiase, by heat, that the loss in activity was greater if measured by the decrease in velocity of hydrolysis of raffinose, than if the loss was determined by means of sucrose. For example, a preparation suffered a loss of 58 per cent in activity with respect to the hydrolysis of sucrose, while based on the change in activity towards raffinose the loss amounted to 75 per cent. In this inactivation, the active invertase remaining did not appear to be altered in kind or in its catalytic behavior. It still continued to conform to the Nelson and Hitchcock equation (74) for normal yeast invertase, and was still retarded normally by α-methylglucoside.

Certain definite conditions seem to be necessary, judging from experience so far, for bringing about this difference in degree of activity of the enzyme preparations for the two sugars. In the first place, the pH of the invertase solution, while it is being heated, must be in the neighborhood of 5.6, and secondly, the temperature of the inactivation must not be lower than 58–60°C. Inactivation of invertase solutions at pH = 4.5 showed none of the difference.

This phenomenon does not seem to be limited to yeast invertase. Simons (93), in this laboratory, has observed the same behavior on inactivating emulsin. Here again, the enzyme lost the most activity with respect to the substrate (β-methylglucoside) which it hydrolyzes at the slowest rate. An aqueous solution (pH = 7.1) of a preparation of emulsin, from almonds, was heated for 18 minutes at 60°C. The loss in activity, calculated from the decrease in the rate of hydrolysis of salicin, amounted to 77 per cent. When the loss was calculated from the decrease in the rate of hydrolysis of β-methylglucoside, it amounted to 90 per cent. So far, however, it has not been possible to interpret these results in any way that would aid in our understanding of enzymes. It is not very probable that the emulsin contained two enzymes β-glucosidase and salicinase, which were inactivated to different extents. This would mean that emulsin, which hydrolyzes so

many of the naturally occurring glucosides, contains a large number of different β-glucosidases, which is highly improbable.

Weidenhagen (105) mentions two instances of enzyme behavior which possibly may be related to the variation in activity with respect to different substrates. The β-glucosidase in emulsin preparations hydrolyzes salicin eight times faster than it does cellobiose, while the β-glucosidase from yeast splits cellobiose faster than it does salicin. The second case is the difference between the pH-activity (figure 1) curves for the two α-glucosidases, one occurring in malt and the other in yeast autolysate. He considers this difference to be due very likely to the colloidal carrier or material accompanying the enzymes, since these might vary in kind depending on the particular source from which the enzyme is obtained.

Many attempts have been made to derive a mathematical expression for representing the course of the reaction when cane sugar is hydrolyzed by invertase, but so far none of them has met with much success (39, 3, 101, 4, 6). Since the velocity of hydrolysis is dependent not only on the concentration of sucrose, but also on the concentrations of the several mutameric hexoses formed during the progress of the reaction, the difficulties encountered in such an attempt are obvious. Even the question as to whether all invertase preparations hydrolyze sucrose in the same way, kinetically, presents itself. Nelson and Hitchcock (74) followed the course of the reaction for a series of 10 per cent sucrose solutions, hydrolyzed by eight different yeast invertase preparations. By properly adjusting the time scales of the curves, figure 7, representing these hydrolyses, they found that five of them could be made to coincide.[5] This shows that these five preparations catalyzed the hydrolysis of the sucrose in the same way. Experience since then has shown that most preparations of invertase obtained from *Saccharomyces cerevisiae*, i.e., ordinary brewer's yeast, give hydrolysis curves that coincide, and hence such preparations have been designated as normal. The degree of purification does not seem to affect this characteristic of yeast invertase.

[5] The adjustment of the time scales was necessary because the invertase preparations used were of unequal strength or activity.

In order to recognize more easily whether a preparation is normal or not, Nelson and Hitchcock made use of the empirical equation

$$\frac{1}{N}\left[\log\frac{100}{100-p} + 0.002642\,p - 0.00000886\,p^2 - 0.0000001034\,p^3\right]$$

in which p represents the per cent hydrolyzed at the time t, while N is a constant, the magnitude of which depends on the activity
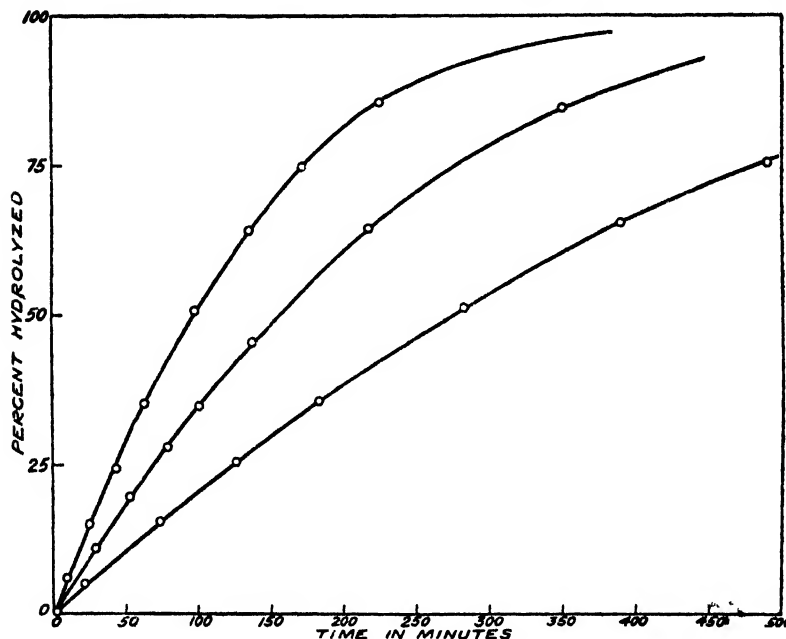

FIG. 7. PER CENT OF SUCROSE HYDROLYZED PLOTTED AGAINST TIME IN THE CASE OF NORMAL YEAST INVERTASE

Nelson and Hitchcock: J. Am. Chem. Soc. **43**, 1632 (1921)

of the preparation used.   In table 2 the experimental data from two yeast invertase preparations, one normal and one abnormal, are given, as well as the corresponding values for the constant, N.

Besides the Nelson and Hitchcock equation being a characteristic property of yeast invertase, Fassnacht (29) finds in the case of normal invertase that the rate of hydrolysis of a 10 per

cent sucrose solution is lowered 73 to 80 per cent by 1 per cent of α-methylglucoside, while the retardation in the case of abnormal preparations is less, usually not over 60 per cent.

Abnormal invertase preparations, like the three observed by Nelson and Hitchcock, occur once in a while in preparing invertase from brewery yeast. Just what produces them is hard to say. Nelson and Hollander (76) found that in some instances the abnormal behavior could be attributed to instability. Invertases

TABLE 2

Data from a normal and an abnormal yeast invertase preparation

NORMAL PREPARATION*			ORMAL PREPARATION†		
Time	Inversion	$N \times 10^6$	Time	Inversion	$N \times 10^6$
minutes	*per cent*		*minutes*	*per cent*	
0	—	—	0	—	—
50	11 50	164	5	3 20	450
100	22.30	163	10	6 35	449
150	32 44	166	15	9 44	448
200	42 44	164	22	13 65	445
250	50 97	163	30	18 46	446
300	59.10	164	60	34 96	440
350	66 23	165	90	49.38	436
400	71 83	164	120	61 48	433
			180	78.81	431
			300	93.59	426

* Normal yeast invertase preparation. Data taken from dissertation of Miss H. Carmichael. Columbia University, 1930.

† Abnormal yeast invertase preparation. Data taken from Nelson and Hitchcock's article.

prepared from sources other than yeast do not conform to the Nelson and Hitchcock equation. In figure 8 is shown the curve (time against per cent hydrolyzed) for a 10 per cent sucrose solution hydrolyzed by an invertase preparation from honey (77). It can be seen that the first part of the curve shows an accelerating effect, which is followed by a gradual falling off in velocity as the reaction proceeds. This acceleration in the earlier part of the hydrolysis is very likely due to the influence of β-glucose mentioned on an earlier page of this paper. Weidenhagen (104) finds

that the curve (time against per cent hydrolyzed) for taka-invertase is different in shape from that of the corresponding curve for yeast invertase.

Mrs. Palmer (90) has compared, with respect to the constancy of N of the Nelson and Hitchcock equation and the extent of retardation by 1 per cent α-methylglucoside, the hydrolyses of a series of sucrose solutions by invertase preparations obtained
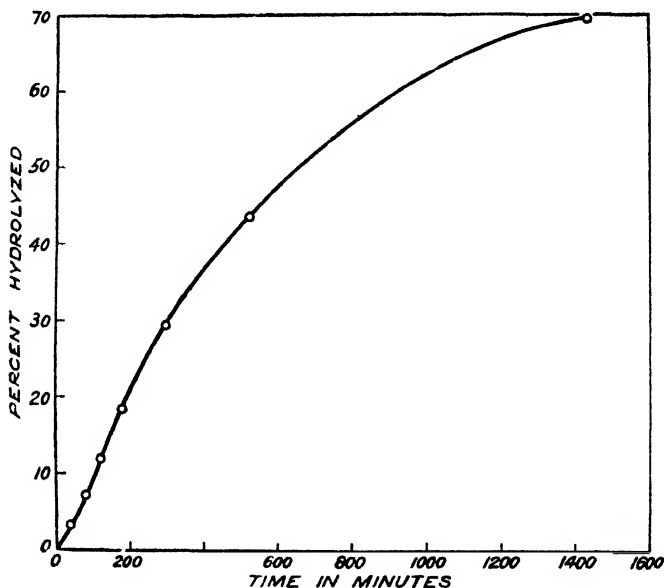

FIG. 8. PER CENT OF SUCROSE HYDROLYZED PLOTTED AGAINST TIME IN THE CASE OF HONEY INVERTASE

Nelson and Cohn: J. Biol. Chem. **61**, 193 (1927), table 3

from yeasts other than *Saccharomyces cerevisiae,* from raisins, and from taka-diastase preparations (*Aspergillus oryzae*). All of these preparations contain the enzyme (or enzymes) which, according to Weidenhagen's classification, has been termed β-*h*-fructosidase. It can be seen in table 3 that some of these hydrolyses differ quite noticeably from the hydrolysis by yeast invertase preparations (*S. cerevisiae*).

The decreases in the values for N were not nearly so pronounced for the enzyme preparations from the yeasts, *S. validus* and *Monilia* as they were for the preparations from raisins and taka-diastase (*Aspergillus oryzae*). Whether this is due to the two yeasts being more closely related genetically to the *S. cerevisiae* than the raisins or the *Aspergillus oryzae* is difficult to say.

The two characteristics of yeast invertase, its conformation to the Nelson and Hitchcock equation and the 73 to 80 per cent retardation by α-methylglucoside, are not easily affected by partially destroying the activity of the enzyme. Miss Carmichael (10) partially inactivated normal yeast invertase preparations by low concentrations of nitrous acid, but was unable to detect any

TABLE 3

Hydrolysis of sucrose solutions by various invertase preparations

	N OF THE N AND H EQUATION	RETARDATION BY α-METHYL-GLUCOSIDE
		per cent
S. cerevisiae...............................	Constant	82
S. ellipsoidens..	Constant	65
S. validus	Decreasing +	81
S. pastorianus...	Constant	77
Monilia	Decreasing +	81
Raisins........	Decreasing ++	Slight
Taka-invertase	Decreasing +++	6

change in these characteristics in the remaining active invertase. Likewise, when the preparations were inactivated to 60 to 75 per cent by heating at 60°C., the remaining active enzymes behave normally, at least within experimental error. Euler, Josephson, and Myrbäck (27) also report that they were unable to detect any difference in the catalytic behavior of yeast invertase preparations when these were partially inactivated by heat.

Doby (12) and coworkers have studied the effect on the invertase in *Penicillium glaucum* due to the absence of certain mineral elements in the food for the organism. They claim that the lack of potassium in the nutrient medium not only diminishes the invertase content but affects its catalytic behavior. Thus the

curve (time against per cent hydrolyzed) plotted from results obtained by hydrolyzing sucrose with the invertase prepared from the potassium-starved organism does not coincide with the corresponding curve for the enzyme preparation from the *Penicillium* grown on a complete diet.   More recently (13), they find that the absence of calcium, magnesium, and phosphates also decreases the invertase content, but apparently does not influence the shape of the hydrolysis curve.   The lack of potassium in the soil also, according to these investigators (11), affects the invertase in sugar beets in much the same way that it does the invertase in the *Penicillium glaucum*.

Fassnacht (29) has studied also the effect on the invertase by varying the nutrient media for yeast, by inoculating the following medium

Malt syrup, 7° Balling.	3 liters
Primary ammonium phosphate	36 grams
Potassium chloride	. 3 grams
Magnesium sulfate	. 3 grams
Calcium sulfate..	3 grams
Cane sugar	. 600 grams
Water	6 liters

with a commercial yeast, which was known to yield normal invertase preparations on autolysis.   The new growth yielded preparations which behaved abnormally and were retarded only 65 per cent instead of 78 per cent by α-methylglucoside.   However, when the same yeast was grown in a medium similar to the one above except that it contained 8 grams of ammonium carbonate in place of the malt syrup, an invertase preparation was obtained that was practically normal.   Therefore it seems that, although it is possible to affect the catalytic behavior of yeast invertase by growing the yeast under certain conditions, we still need more data before anything definite can be said about these conditions.

So far the discussion has dealt with invertase as it exists and acts outside of the living cell.   The question may be asked whether the information accumulated by the study of cell-free preparations of the enzyme also holds for the behavior of the

enzyme when it acts within the cell where conditions undoubtedly are quite different. Linderström-Lang and Holter (61) state: "It is actually only the study of the action of typically secretion enzymes, outside of the cells, that experiments *in vitro* may be considered with certainty to reproduce the processes taking place
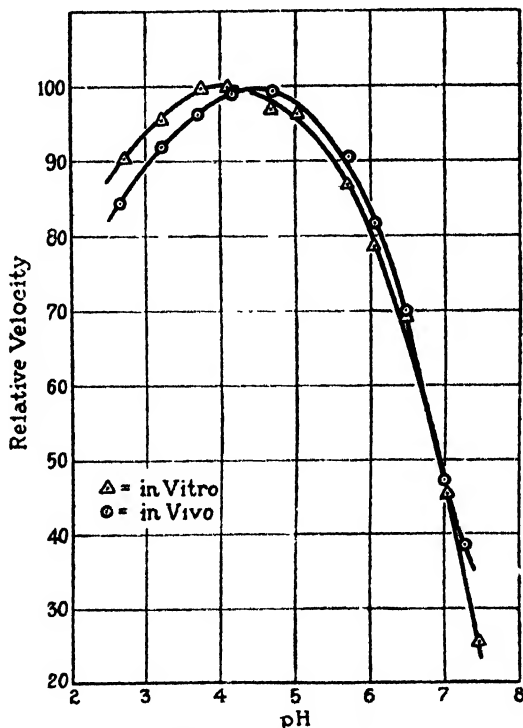

FIG. 9. COMPARISON OF THE pH-ACTIVITY RELATIONSHIPS WHEN A CELL-FREE INVERTASE PREPARATION AND LIVING YEAST CELLS WERE USED TO HYDROLYZE SUCROSE

Wilkes and Palmer: J. Gen. Physiol. **16**, 233 (1932)

in the organism." Yeast invertase is an intracellular enzyme, and is not secreted by the organism. The only way it can be separated from the cell and brought into solution is by breaking down the latter by autolytic reactions. Since, however, live yeast cells also hydrolyze sucrose, it is possible to study the kinetics of the enzyme's activity *in vivo*.

As early as 1911, Euler and Kullberg (17) attempted to compare the hydrolysis of sucrose by live cells with the reaction brought about by yeast invertase preparations, using the monomolecular constants as a measure of the enzyme's activity. Similar, though not identical, results were obtained in the two cases. Recently, Nelson, Palmer, and Wilkes (83) have compared the two reactions
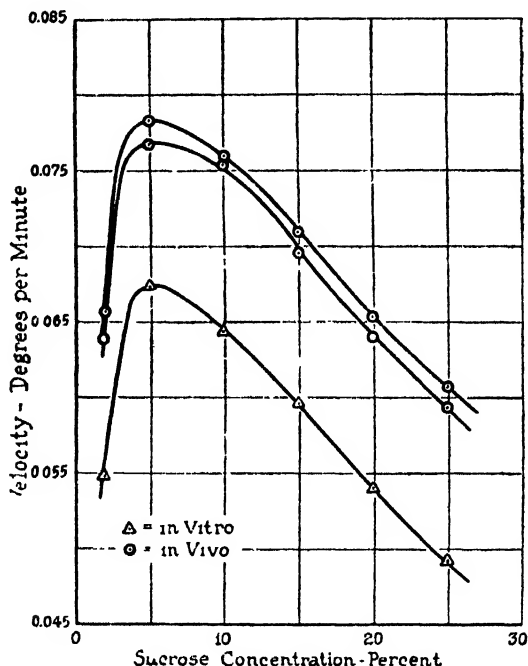
FIG. 10. COMPARISON OF THE CHANGES IN ACTIVITY WITH CHANGES IN SUCROSE CONCENTRATION WHEN A CELL-FREE INVERTASE PREPARATION AND LIVING YEAST CELLS WERE USED TO HYDROLYZE SUCROSE

by means of the Nelson and Hitchcock equation and find that the hydrolysis by the live cells also gives constant values for N, just as in the case of the cell-free preparations. In other words, as far as the course of the hydrolytic reaction is concerned, yeast invertase hydrolyzes sucrose in the same way whether it occurs in the live yeast cell or is first removed from the cell by autolysis.

The kinetics of the hydrolysis of sucrose by live cells has also

been compared (106, 84), in this laboratory, with that by invertase preparations in two other respects, viz., the pH-activity relationship and the influence of varying concentrations of sucrose and water. The results obtained are shown graphically in figures 9 and 10. In both of these comparisons it is evident that it makes practically no difference whether the enzyme is acting *in vivo* or *in vitro*; the results are the same, as is shown by the similarity of the corresponding curves.

These similarities in behavior between the invertase in the live cell and the invertase as it occurs in the cell-free preparations, brings out the interesting question as to just where in the living cell the active enzyme is located. If we regard the structure of the yeast cells as consisting of a central fluid, the cell sap, contained in various vacuoles, surrounded by a cytoplasmic layer containing protein bodies and the cell nucleus, and bound externally by a cellulosic wall, we define at least four distinct regions in which the enzyme may act, viz., in the cell sap, in the surrounding cytoplasmic layer, at the external surface of the cytoplasm, or on the inner or outer surfaces of the cell wall. According to Small (94) one would expect the pH of the cytoplasmic layer to remain fairly constant, not varying over a wider range than 1 unit in the pH scale. The results indicated in figure 9 would therefore eliminate this part of the cell as the seat of the invertase activity. The fact that when a given weight of yeast cells is placed in hypertonic sugar solutions, the weight of the yeast decreases as the sucrose concentration increases, indicates plasmolysis (35). The latter is therefore an argument against the sugar and water concentrations within the cell sap being the same as those in the outside medium in which the yeast cells are suspended. Hence the results indicated in figure 10 exclude the cell sap as being the place where the enzyme is acting on the sucrose. The elimination of the cell sap and the cytoplasmic layer leaves only the external surface of the cytoplasm or the inner or outer surfaces of the cell wall as the possible seat of the active invertase. In other words, the active invertase in the yeast cell is very likely located close to the outer surface of the cell.

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THE CHEMISTRY OF THE ALKALI AMIDES

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CONTENTS

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PART I. PREPARATION, STORAGE, AND INORGANIC REACTIONS

I. INTRODUCTION

The history of science is filled with numerous examples of laboratory or museum curiosities which became after a time common laboratory reagents or commercially useful substances. Such in a general way has been the case with the alkali amides, compounds known for well over a hundred years, but which, with the exception of occasional isolated and sporadic researches, remained without systematic investigation for perhaps ninety years following their discovery. Then arose a period of active and far-reaching research which continues unabated today. Sodium amide has become a much used reagent in synthetic organic chemistry because of its ability to promote condensation

reactions, to introduce amino groups into a molecule, and to remove the elements of water or of a hydrohalide acid. Moreover, the use of the alkali amides for the commercial production of indigo, cyanides, and azides has resulted in a rapid growth of the literature dealing with the alkali amides. So much work has now been done in this field that anyone desirous of acquainting himself with the chemistry of the alkali amides is faced with a tremendous task. It is the purpose of this article to give a review of the chemistry of the alkali amides in as brief a manner as is consistent with thoroughness and accuracy.

II. HISTORICAL

The discovery of sodium and potassium amides[1] belongs rightly to that golden age of chemical development, the early part of the nineteenth century. At that time chemistry was in a state of flux. The elementary nature of chlorine had as yet not been established and many substances now known to be compounds were regarded as elementary in nature. In 1807 Davy (22) electrolyzed the supposed elements, soda and potash, and obtained sodium and potassium. This discovery immediately caused considerable discussion and speculation and likewise precipitated a good deal of experimentation. Gay-Lussac and Thénard (55, 56) held that the new substances were compounds of hydrogen with soda and potash and showed that these metals could be prepared in quantity much more easily by the reaction of iron with the hydroxides. During the course of their examination of the properties of these newly found alkali metals, Gay-Lussac and Thénard (57, 58) examined their reaction with ammonia and first prepared sodium and potassium amides. They found in these substances a proof for their views concerning the nature of sodium and potassium, because in their experiments on the preparation of the amides and subsequent hydrolysis they obtained a volume of hydrogen greater than that of the ammonia with which they began; this experimental error may very likely have arisen from the incomplete conversion of the

[1] The names "sodamide" and "potassamide" are not used here because it is felt that the general usage of such contractions would be confusing.

metal to the amide. Davy (23) worked with these compounds at the same time as Gay-Lussac and Thénard and saw in his work the confirmation of his view that the volatile alkali, ammonia, like the solid alkalis contained oxygen. It is interesting that the first two investigations upon the alkali amides led their pursuers to erroneous conclusions which had soon to be abandoned.

Gay-Lussac and Thénard (58) later arrived at the formulas $NaNH_2$ and KNH_2 for sodium and potassium amides by indirect analysis, while Beilstein and Geuther (2) made the first direct analyses of sodium amide. Titherley (96) made a thorough study of the composition of these substances by synthetical methods. Gay-Lussac and Thénard (58) called the substances which they obtained "ammoniures," while Davy seems to attach no name to the amides in his papers. Beilstein and Geuther speak of sodium amide but they do not claim the nomenclature as their own; they speak, instead, of some earlier work of Wöhler and Kolb on sodium amide, but give no reference. The amides of lithium (79, 96), rubidium (98), and cesium (83) have also been prepared. One group of investigators, including Titherley, Dennis and Browne, and others, have studied the preparation of the alkali amides from the molten metals and gaseous ammonia, while another group, including in part Joannis, Ruff, Franklin, and Kraus, have investigated the action of liquid ammonia upon the alkali metals.

The chemistry of the alkali amides has been the subject of a large number of investigations. Davy (24) studied in a superficial manner the reaction of potassium amide with tellurium and arsenic. Gay-Lussac and Thénard (58) found that several metals were attacked by potassium amide. The next workers in this field were Beilstein and Geuther (2), who investigated the action of sodium amide on carbon monoxide, carbon dioxide, and carbon disulfide; Baumert and Landolt (1), who studied the reactions of sodium amide with some simple organic substances; and Drechsel (27), who reinvestigated the reaction of carbon dioxide with sodium amide and established the steps.

In the last decade of the nineteenth century there were several

investigations upon the alkali amides, which are recorded in the publications of Joannis (64), Wislicenus (103) (use in preparing sodium azide), Titherley (96 to 98), and Moissan (79), as well as patent literature bearing upon the use of amides as intermediate products in the manufacture of cyanides (115). The first decade of the twentieth century saw the beginning of the use of sodium amide in organic syntheses as recorded in the papers of Haller and Bauer (61), Claisen (20), Lebeau (73), Meunier and Desparmet (77), and Sachs (88), as well as important contributions to the inorganic chemistry of the amides through the work of Franklin (36 to 41), Kraus (67), Winter (102), Dennis and Browne (26), and Ephraim (29).

In 1918 Wöhler and Stang-Lund (104) published an important paper bearing upon the ionization and electrolysis of the fused alkali amides. Other papers of the decade were those of Stollé (93), Chablay (17), Chichibabin (18), and Miles (78).

In 1923 the senior author (3 to 12) began a series of researches upon the reactions of the elements with the alkali amides in liquid ammonia solution. Contemporaneous papers were those of McGee (76), Wibaut (101), Picon (82), Bourguel (15), Seide (92), Verley (99, 100), and Guntz and Benoit (60). The most recent work on the reactions of the fused amides is that of Fernelius and Bergstrom (31) and of Fulton and Bergstrom (54), who employed a number of refinements and special precautions in their studies.

III. THE ALKALI AMIDES AS THE CAUSTIC ALKALIS OF THE AMMONIA SYSTEM

That theory which best serves to explain and classify the reactions of the alkali amides is the conception of an ammonia system of compounds. Franklin's ideas in this connection are sufficiently well-known so that it is necessary here only to recall a few of the major points of Franklin's thesis: first, that water and ammonia are abnormal in their properties when compared to the hydrides of the other elements in groups six and five, respectively, of the periodic table, and that both water and ammonia are good solvents of a polar character; second, that, whereas the familiar

salts, acids, and bases are compounds of oxygen which may be regarded either as substituted water molecules or dehydration products of substituted water molecules, there are numerous nitrogen compounds which may in a similar manner be regarded as derivatives of ammonia, and these substances constitute the salts, acids, and bases of the ammonia system of compounds (38, 118 to 122). Franklin distinguishes between the representatives of these two systems of compounds by calling the first *aquo* salts, etc., and the latter *ammono*. Furthermore, it is to be understood that the best solvent for the study of the representatives of the ammonia system is anhydrous liquid ammonia.

Whenever an alkali metal reacts with water a strong base and hydrogen result through a vigorous reaction:

$$2Na + 2H_2O \longrightarrow 2NaOH + H_2$$
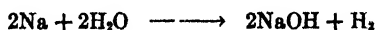
It is customary to say that the alkali metal has displaced one of the hydrogen atoms of water. Similarly, the alkali metals displace hydrogen from ammonia to produce an alkali amide:

$$2K + 2NH_3 \xrightarrow{\text{catalyst}} 2KNH_2 + H_2 \quad \cdot$$
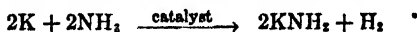
This similarity in the formation of an amide and an hydroxide suggests that the alkali amides are the strong bases of the ammonia system. All that is known about the basic amides is consistent with this view.

Action on indicators: neutralization reactions

In liquid ammonia solution, the alkali amides effect the same color changes in indicators as do the alkali hydroxides in aqueous solution. Thus the addition of a very small amount of a liquid ammonia solution of potassium amide to a neutral colorless solution of phenolphthalein in the same solvent immediately turns the solution a deep red (36, 38). A colorless solution of triphenylmethane similarly develops a deep red color, owing to the formation of a colored salt (71). Liquid ammonia solutions of safranine are red (53) in color but become blue in the presence of potassium amide. Carmine and alizarin also exhibit color changes in solutions of these ammono bases (36). A yellow

solution of an aromatic hydrazo compound in liquid ammonia is colored dark brown by the addition of a drop of potassium amide solution (91).

Closely associated with the ability of the alkali amides to affect the colors in indicators is the production of salts by the neutralization of acids by these ammono bases. This property was first investigated by Franklin and Stafford (37), who prepared the potassium and dipotassium sulfamides, $O_2S(NH_2)NHK$ and $O_2S(NHK)_2$. A large number of salts of organic ammono and mixed aquo-ammono acids have been made by the use of the alkali amides. These will be discussed in Part II of this paper.

Precipitation of insoluble bases

Just as potassium hydroxide acts on metallic salts in solution in water to form insoluble metallic hydroxides or oxides, as the case may be, so potassium amide added to liquid ammonia solutions of the salts of heavy metals gives, in certain instances, precipitates of the amides, in others of the imides, and in still others of the nitrides. The following equations representing the formation of barium amide, lead imide, and mercuric nitride illustrate this behavior of the alkali amides:

$$Ca(NO_3)_2 + 2KOH \longrightarrow \underline{Ca(OH)_2} + 2KNO_3$$
$$Ba(SCN)_2 + 2KNH_2 \longrightarrow \underline{Ba(NH_2)_2} + 2KSCN \ (49)$$
$$PbI_2 + 2KNH_2 \longrightarrow \underline{Pb{=}NH} + NH_3 + 2KI \ (38)$$
$$Hg(NO_3)_2 + 2KOH \longrightarrow \underline{HgO} + H_2O + 2KNO_3$$
$$3HgI_2 + 6KNH_2 \longrightarrow \underline{Hg_3N_2} + 4NH_3 + 6KI \ (38)$$
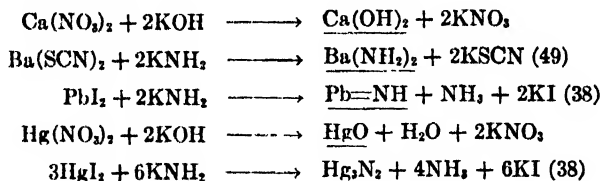
Other amides, etc., prepared by similar reactions are the following: Cu_2NH and Cu_3N (34, 45); silver amide, $AgNH_2$ (38); impure cadmium amide, $Cd(NH_2)_2$ (14); thallous nitride, Tl_3N (44); bismuth nitride, BiN (38); manganous amide, $Mn(NH_2)_2$ (4); impure ferrous nitride, Fe_3N_2; ammonous cobaltous nitride, $Co_3N_2 \cdot xNH_3$ (5); and nickelous amide, $Ni(NH_2)_2$ (14). Attempts to prepare the amides of beryllium (10), aluminum (12, 38, 47), and chromium (14) by this method have been unsuccessful.

Amphoteric amides

Just as certain metallic hydroxides such as those of zinc, lead, and aluminum dissolve in aqueous solutions of potassium hydroxide to form potassium zincate, plumbite, and aluminate, respectively, so zinc amide (34), lead imide (38, 42), and ammonous aluminum nitride (12) are acted upon by potassium amide in liquid ammonia solution to form the analogous ammono salts, potassium ammonozincate, ammonoplumbite, and ammonoaluminate:

$$2H_2O + Zn(OH)_2 + 2NaOH \rightarrow Zn(ONa)_2 \cdot 4H_2O$$
$$Zn(NH_2)_2 + 2KNH_2 \rightarrow Zn(NHK)_2 \cdot 2NH_3$$
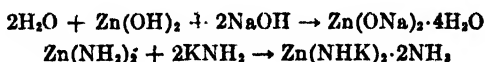
It will be recalled that because of the hydrolyzing action of water on salts of weak acids, the preparation of alkali metal aluminates, zincates, and plumbites is attended with serious manipulative difficulties.

In sharp contrast to the behavior of water solutions of the aquo salts it has been found that from liquid ammonia solutions the analogous ammono salts may be easily obtained, for the most part beautifully crystallized and of definite composition. It is a matter of much interest furthermore to observe that whereas, on the one hand, a very limited number of metallic hydroxides react after the manner of aluminum hydroxide with potassium hydroxide in aqueous solution, on the other hand, the number of metallic amides which react with potassium amide in liquid ammonia is very large. Not only have an ammonoaluminate, $Al(NH_2)_2NHK \cdot 2NH_3$, an ammonozincate, and an ammonoplumbite, $PbNK \cdot 2.5NH_3$, of potassium been prepared, but the list of such compounds has been extended to include the following: a cadmiate, $Cd(NHK)_2 \cdot 2NH_3$ (14); a cuprite, $CuNK_2 \cdot 3NH_3$ (34, 45); an argentate, $AgNHK \cdot NH_3$ (48); a hypomanganite, $Mn(NHK)_2 \cdot 2NH_3$ (4); a thallite, $TlNK_2 \cdot 4NH_3$ (44); a nickelite, $KN(NiNK_2)_2 \cdot 6NH_3$ (14); a berylliate, $Be(NH_2)NHK \cdot NH_3$ (10); a cerite, $Ce(NHK)_3 \cdot 3NH_3$; a lanthanite, $La(NHK)_3 \cdot 3NH_3$ (6); a titanate, $NTiNHK$ (43); a molybdite, $Mo(NK)_2NH_2$; a tungstite, $W(NK)_2NH_2$ (7); a magnesiate, $Mg(NHK)_2 \cdot 2NH_3$ (46); a bariate, $BaNK \cdot 2NH_3$; a strontiate, $SrNK \cdot 2NH_3$; a calciate.

CaNK·2NH$_3$ (49); and even a sodiate, NaNK$_2$·2NH$_3$, and a lithiate, LiNK$_2$·2NH$_3$ (50). Sodium ammonoberylliate, Be(NH$_2$) NHNa·NH$_3$ (10), sodium ammonomagnesiate, Mg(NHNa)$_2$· 2NH$_3$ (8), sodium ammonoaluminate, Al(NH$_2$)$_2$ NHNa·NH$_3$ (3, 4), and sodium ammonostannite, SnNNa·2NH$_3$ (9), are also known, as well as two rubidium ammonosodiates, NaNHRb·NH$_3$ and NaNRb$_2$·2NH$_3$, and a rubidium ammonolithiate, LiNHRb· NH$_3$ (50).

Ammonobasic salts

Occasionally the addition of a base to an aqueous solution of a salt results in the precipitation not of an hydroxide or an oxide but of a basic salt. Nitrogen compounds analogous to basic salts, which may for convenience be called ammonobasic salts, are sometimes formed upon the addition of a soluble ammono base, such as potassium amide, to an ammonia solution of a salt. Ammonobasic salts so prepared are the following: NH$_2$HgCl; Hg$_2$NCl; Hg$_2$NBr; Hg$_2$NI; Pb$_2$NI·NH$_3$ (38, 39); Al(NH$_2$)$_3$· AlI$_3$·6NH$_3$ and Al(NH$_2$)$_3$·Al(NH$_2$)$_2$I·NH$_3$ (47); as well as certain ammonobasic salts of beryllium (10, 11), such as 3Be(NH$_2$)$_2$· BeBr$_2$·4NH$_3$ and 5Be(NH$_2$)$_2$·BeI$_2$·4NH$_3$, which are best made by the action of an ammonium salt on an excess of metallic beryllium in liquid ammonia.

The above discussion should serve to show that the alkali amides may be regarded as the caustic bases of the ammonia system of compounds. Before proceeding with a detailed account of the reactions of the elements with the alkali amides and of the reactions of the latter substances in the fused state, it seems advisable to treat such subjects as the preparation, preservation, and physical properties of the amides.

IV. PREPARATION OF THE ALKALI AMIDES

When the alkali amides are desired in any but the smallest amounts, they are best made by the reaction of gaseous ammonia upon the molten metal. Great care must be taken when using this method of preparation both to use pure materials and to exclude all air and moisture during the interaction of metal and ammonia and during the storage of the amide. Convenient

arrangements of apparatus for carrying out this synthesis are described in the papers of Dennis and Browne (26), Kraus and Cuy (70), Fernelius and Bergstrom (31), and Fulton and Bergstrom (54). The metal, sodium or potassium, contained in a nickel crucible, first melts to a silvery liquid with a high surface tension that does not wet the sides of the container. As the reaction begins small green-blue drops form on the surface of the metal and dart about for a time before sinking to the bottom of the vessel. These drops are thought to be a solution of metal in the amide.[1] As the reaction continues, the metal floats about on the denser amide, oftentimes, as the drops of metal become small, moving about rather rapidly. All the while the amide remains green-blue in color, more particularly in the region immediately in contact with the metal. Finally, all of the metal disappears and shortly afterward the liquid becomes clear light yellow in color. The melt now consists of pure amide and will set, on cooling, to a white, crystalline solid.

Mention was made above of the care necessary in obtaining pure materials from which to generate the amides. Investigators until very recent years have taken elaborate precautions to obtain pure ammonia. With the present wide-spread use of liquid ammonia and the ease of obtaining this substance in steel tanks no such precautions are necessary. Ammonia distilled from a tank in which a few grams of sodium has been dissolved as a drying agent gives a very pure amide (36, 65). The sodium or other metal that is used to generate the amide must be relatively free from oxide, hydroxide, moisture, etc. Dennis and Browne (26) advise cutting the sodium from the center of large sticks so that the metal will be free from the hydrocarbon in which it has been preserved, and to warm all apparatus with which the sodium is to be brought in contact in order to drive off the film of moisture that is present at ordinary temperatures. Where small amounts of very pure amide are desired, they are

[1] The alkali and alkaline earth metals as well as magnesium dissolve in liquid ammonia to give blue solutions. Likewise solutions of lithium in methyl- and ethyl-amines, of potassium in ethylenediamine, and of cesium in methyl- and ethyl-amines are all blue in color (67,123,124). Finally sodium dissolves in fused sodium hydroxide to give a blue solution (31).

best prepared by melting the metal in an ammonia atmosphere and filtering from the oxide crust, etc., through a fine capillary (30, 31, 54). Several different reaction vessels have been used for the conversion of the alkali metal to amide, but those constructed of nickel appear to be the most generally useful. Vessels of glass, porcelain, etc., although used in several cases (29, 76, 103) are out of the question because they are attacked by the melt and hence give a contaminated product. The reports on the action of the fused amides on various metallic vessels are somewhat conflicting. Titherley (96) found that platinum was only slowly corroded by sodium amide, but after a week's use the metal becomes friable and much corroded. Dennis and Browne (26) report that the action is very marked, and McGee (76) states that platinum dissolves with evolution of ammonia. Titherley (96; cf. 29) used silver boats for his studies of lithium, sodium, potassium, and rubidium amides and reported that the fused amides have no appreciable action on the silver. Dennis and Browne (26), however, found that sodium amide attacks a silver crucible to such an extent that the melt adheres firmly to the sides of the crucible on cooling. Winter (102) reports that a silver-plated crucible is rapidly attacked by sodium amide. Miles (78) used a silver boat in his experiments with sodium amide but he did not work above 300°C. Ruff and Goerges (86) also used silver dishes for heating lithium amide and lithium imide between 360°C. and 450°C. Wöhler and Stang-Lund (104) used a silver-nickel element for temperature measurements in fused sodium and potassium amides and found that it was not acted upon chemically. They state that only iron and nickel are sufficiently resistant at 220°C. for a study of the anode gases when electrolyzing the above amides. Titherley (96) suggested the use of a polished iron retort for preparing the amides in large quantity and De Forcrand (25) made sodium amide in iron dishes. The use of iron vessels is open to some objection, however, because the carbon in this metal introduces cyanides into the amide (26, 95), and because all iron vessels become rusty in time. On the other hand, Winter (102) seems to have had good success using a pure wrought iron crucible for preparing sodium amide.

Following the recommendations of Dennis and Browne, nickel vessels have been used in the laboratories of Stanford University for several years with entire success (19, 62, 66, 81; cf. 31, 60). Although the pure sodium and potassium amides of themselves do not attack nickel, there are formed frequently, by the reaction of substances introduced into the melt, mixtures which do etch and discolor the nickel boats, sometimes badly (31). Franklin (51) has on occasion used a gold crucible with satisfactory results. The authors from their own experience would place monel metal second only to nickel as an amide fusion vessel, leaving gold out of consideration because of its cost. Although copper is not attacked by sodium amide, its use as a containing vessel seems never to have been investigated. In any event, air and moisture would have to be carefully excluded both during conversion of the metal and storage of the amide, because a mixture of moist air and ammonia attacks copper.

Temperature is a very important factor in the conversion of alkali metals to the amides. In the case of sodium amide, this factor has been rather carefully studied.

"The rapidity of action of the ammonia upon the molten sodium was found to increase with the temperature, as was to be expected. But at temperatures much above 350° (which was the temperature found on the whole to give the best practical results) there seems to be some loss of the product by sublimation. This was noted also by Titherley, who worked chiefly between temperatures of 300° and 400°. At temperatures below 250°, on the other hand, rather curious results were obtained in our work. Although in every case the reaction seemed to have been completed, analysis invariably showed too low a percentage of nitrogen, and too high a percentage of sodium. Moreover, the deficit of nitrogen and excess of sodium showed a tendency to increase as the temperature became lower. At first this was attributed to the possible presence of uncombined sodium dissolved in the amide; but when pieces of the product were thrown upon water beneath an inverted glass tube filled with water, no hydrogen was liberated." (26)

Certainly these authors are slightly in error in their last statement. Winter (102) examined numerous specimens of sodium amide and found that all of them gave hydrogen and some

nitrogen upon reaction with water.   This behavior had previously been noted by Davy (23) in the case of potassium amide.   The ratio between hydrogen and nitrogen depends not only on the way in which the sodium amide is prepared, but also on the length of time and manner in which it is kept previous to analysis. Furthermore, Winter found that "the relative proportion of nitrogen to hydrogen is low in sodamide that has been insufficiently heated, but high in sodamide properly prepared."

The keynote to an explanation of these anomalous results was sounded in a recent paper by Guntz and Benoit (60).   Following an accident caused by sodium amide in their laboratory, they examined specimens of commercial sodium amide and found them to contain from 1.85 to 11.75 per cent of sodium hydride.   They found, also, that in making sodium amide if the melt be cooled before all of the sodium has disappeared, it contains as much as 3 to 6 per cent of sodium hydride.   Miles (78) had previously shown the reaction,

$$\text{NaNH}_2 + \text{H}_2 = \text{NaH} + \text{NH}_3$$

to take place in a stream of hydrogen between 200°C. and 300°C. Guntz and Benoit showed that this reaction is reversible in a stream of ammonia.   Going back to Dennis and Browne's results, let us make the assumption that the presence of sodium hydride is responsible for the high percentage of sodium and low percentage of nitrogen.   Table 1 shows how well this assumption checks with the actual analyses of Dennis and Browne (26). They state in their paper: "In Table I are given the results of three experiments conducted at different temperatures in the neighborhood of the temperature limit below which apparently a good product cannot be obtained.   In the second and third of these experiments, about 100 grams of sodium were employed in each case, while in the first a somewhat smaller amount was used. The method of bubbling (through the molten metal) was used in each case, and the reaction was allowed to proceed to completion."

The first two columns show the results of the analyses of Dennis and Browne.   From the percentage of nitrogen we can calculate the percentage of sodium amide in each sample (column 3) and

by difference the percentage of sodium hydride (column 4). From these values it is possible to calculate further the percentage of sodium as amide (column 5) and as hydride (column 6). The sum of these two partial percentages (last column) should agree with the actual percentage of sodium determined by analysis. The agreement is very close and we may conclude that the formation of sodium hydride is responsible for the impure amide obtained below 250°C.

Winter (102) claimed that the nitrogen which he always obtained upon the hydrolysis of sodium amide arose through the

TABLE 1

	1	2	3	4	5	6	7
	Na	N	NaNH₂	NaH	Na AS NaNH₂	Na AS NaH	TOTAL Na
					per cent	per cent	
Theory for NaNH₂........	58.9	35.9	100.0		58.9	0.0	58.9
Theory for NaH	95 8					95.8	95.8
No. 1, 250°C.	59.4	35 3	98.3	1.7	57 9	1.6	59.5
No. 2, 240°C.....	61.4	33.6	93.6	6.4	55.1	6.1	61.2
No. 3, 200°C.	71.2	23.4	65 2	34.8	38.4	33.3	71.7

oxidation of sodium amide. Probably the nitrogen is generated by the following reaction,

$$NaNO_2 + NaNH_2 = 2NaOH + N_2$$
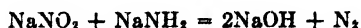
since sodium nitrite is known to be the principal oxidation product of sodium amide (see below). However, the decomposition of sodium amide by water takes place with extreme violence and a sudden local rise in temperature which may be sufficiently high to promote the direct decomposition of some of the amide or of the ammonia liberated in the reaction. When pure sodium amide is slowly hydrolyzed with water vapor no insoluble gases are formed (13, 52). The nitrous oxide observed by Winter (102) to be formed during the acid hydrolysis of sodium amide undoubtedly had its origin in the traces of sodium hyponitrite which this investigator found to be present in specimens of the amide which had been exposed to the air for some time.

For preparing the alkali amides, Kraus and Cuy (70) used gaseous ammonia at a pressure of approximately ten atmospheres in a steel tube. They state that the higher pressure serves to accelerate the reaction between the metal and the ammonia vapor. Dennis and Browne (26) stress the importance of having the largest possible surface of contact between the metal and gaseous ammonia. Bubbling the ammonia through the molten sodium, rather than merely conducting the gas over the surface of the metal, greatly accelerates their interaction. During the formation of the amides, the tendency of these substances to sublime and creep over the sides of the containing vessel is frequently troublesome.

The alkali metals dissolve in liquid ammonia without any chemical action,[3] and such solutions are perfectly stable at low temperatures or over short periods of time. The reaction of the metal with ammonia to form the amide, however, becomes noticeable on long standing or at more elevated temperatures.[4] Joannis (64) observed no appreciable formation of amide with sodium and potassium solutions at $-78°C$. Ruff and Geisel (85) claim that at room temperature half-saturated solutions require the lapse of the following times before they are completely decomposed: Cs, 1 to 2 hrs.; Rb, 6 to 10 hrs.; K, 2 to 3 days; Na and Li, 2 to 3 weeks. Leighton, Bergstrom, and Ogg (74) have, however, prepared in quartz very dilute transparent solutions of cesium in ammonia that could be kept for several days at room temperature without decolorization. The contention of Joannis

[3] There is considerable confusion in chemical literature on this particular point. The erroneous interpretation of vapor pressure data for solutions of the alkali metals in liquid ammonia led Joannis to the conclusion that there existed in such solutions compounds of the type $Na \cdot NH_3$ or $NaNH_3 \cdot NaNH_3$, which he called "metal-ammoniums." Later work has clearly demonstrated that solutions of the alkali metals in liquid ammonia contain no such combinations but are simply solutions of metals. Despite the fact that the death knell of the "metal-ammonium" theory was sounded over twenty years ago, the influence of Joannis and his followers has been so wide-spread that even today one finds references to the "metal-ammoniums" (67,123,124).

[4] The difference in the rate of reaction of the alkali metals with water and with ammonia may be explained as being due to two factors: (1) the greater affinity of the metals for oxygen than for nitrogen, and (2) the much greater concentration of hydrogen-ion in water.

that, in a closed system, the pressure of hydrogen resulting from the conversion of sodium to sodium amide has an inhibiting effect upon the rate of the reaction has been shown by Kraus to be untenable (67). The reactions of the alkali metals with liquid ammonia are greatly influenced by catalysts. Whereas a solution of potassium in ammonia may be preserved for a couple of weeks even at room temperature, in the presence of iron oxide or finely divided platinum the potassium is completely converted to potassium amide within an hour— oftentimes in a very few minutes (38, 85). This catalyzing effect is less with lithium and sodium. Many metals, and metallic oxides and hydroxides serve to catalyze these reactions. The catalytic effect of solid sodium amide makes the conversion of sodium an autocatalytic reaction (67). Short ultra-violet light also catalyzes the reaction of the alkali metals with liquid ammoia (74; cf. 64).

There are numerous patents covering the manufacture of the alkali amides (106 to 113).

V. PROPERTIES OF THE ALKALI AMIDES

The alkali amides are white or translucent, crystalline solids which melt to clear liquids frequently tinged slightly yellow or green. The green and black tints noticed by some of the earlier investigators were due to impurities (boron from glass (?), etc.). All the amides are hydrolyzed vigorously by water according to the following equation,

$$MNH_2 + H_2O = NH_3 + MOH$$
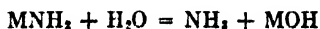
where M is any alkali metal. In accordance with this reaction, Stollé (93) has used sodium amide to obtain anhydrous hydrazine from hydrazine hydrate.

Our knowledge of the physical constants of the amides is very incomplete (table 2), the melting points being about the only constants known with any certainty for all the amides. Probably much of the material given below under the individual substances is in error.

Lithium amide

Lithium amide is a white substance, markedly crystalline, which melts to a clear liquid with a greenish tinge at 380–400°C. It volatilizes somewhat around 400°C. and may be sublimed under pressure in an ammonia atmosphere (96). On heating, lithium amide is decomposed into the imide and ammonia

$$2LiNH_2 \rightarrow Li_2NH + NH_3$$

The reaction begins at 240°C. and is rapid at 450°C. (86). The imide forms a white, partly sintered mass which does not melt at 600°C. but assumes a yellow color. At higher temperatures, it

TABLE 2

Physical constants of the alkali amides

AMIDE	MELTING POINT	DENSITY	HEAT OF FORMATION	SOLUBILITY IN LIQUID AMMONIA
	degrees C.		*calories*	
LiNH$_2$ ...	380–400 (96)*	1.178 (17 5°C.) (86)	86 7 (59)	Insoluble (50)
NaNH$_2$.	210 (76, 104)		33 04 (25)	1 gram per liter (52)
KNH$_2$....	338 (104)			Very soluble (36)
RbNH$_2$ ..	285–287 (98)			Very soluble (50)
CsNH$_2$.. .	260 (83)			Very soluble (83)
Li$_2$NH		1.303 (19°C.) (86)	52 6 (59)	

* The figures in parentheses refer to the bibliography.

decomposes into lithium nitride (m.p. 849°C.). It is very interesting to note that lithium amide is the only alkali amide which is converted into the imide and nitride on heating.

Sodium amide

Sodium amide has been studied to a much greater extent than any other of the amides. Gaseous ammonia reacts very readily with molten sodium at a temperature of 300°C., as described above. The molten amide is clear, usually with a slight yellow tinge. The waxy appearing solid has a conchoidal fracture and a marked crystalline structure. In liquid ammonia, beautiful dodecahedra of sodium amide are easily obtained. Titherley

(96) studied the thermal decomposition of this compound. A little above the melting point the liquid becomes pale green. Between 300°C. and 400°C. the liquid darkens but remains apparently unchanged; at 400°C. the substance begins to volatilize; between 500°C. and 600°C., gas is evolved rapidly, owing to the decomposition of the amide. The gas proved to be hydrogen and nitrogen in the approximate ratio 2:1, with a slight but consistent deficiency of hydrogen from this ratio. Titherley attributed this behavior to the reducing action of hydrogen gas upon glass and to its absorption by sodium. Metallic sodium remains behind after the decomposition or distills off. In a current of ammonia, the sodium formed by the decomposition of the amide reacts with the ammonia so that there is virtually a decomposition of ammonia. There is no tendency to form an imide or nitride either by heating sodium amide alone or with sodium metal. The evolution of ammonia which McGee (76) attributed to a decomposition of sodium amide into imide or nitride undoubtedly had its origin in the reaction of the amide with the glass container and, possibly, also in the reaction with the platinum present.

Sodium amide reacts violently with water. When thrown upon water, a piece of the amide darts about on the surface with a hissing noise much as a piece of sodium. Frequently the amide bursts into flame and after a time often explodes. Sodium amide heated in contact with air catches fire. This substance may be safely hydrolyzed in quantity by first allowing it to react with alcohol and then adding water or by first covering the solid with benzene and then slowly adding water (54).

As the strong bases of the ammonia system, it would seem that sodium and potassium amides dissolved in liquid ammonia should be good conductors of the electric current. The facts are however, that sodium amide is a poor conductor. The reason for this discrepancy is not known (36, 41, 69).

The specific conductivity of molten sodium amide, measured with nickel electrodes at 210°C., is 0.593 mho, and the decomposition voltage is 0.71 volt with the temperature coefficient 1.52 × 10⁻³ (104). The above value of Wöhler and Stang-Lund's for the specific conductivity is probably more accurate than that

found by McGee (76) (1.665 ± 0.005 mho at 210°C.), who used platinum electrodes which were attacked by the melt.   Indeed, these platinum electrodes were dissolved by the amide to such an extent that McGee could not determine accurately the temperature coefficient but could only note qualitatively that it was positive.

Potassium amide

Potassium amide, like its sodium analogue, has formed the subject of numerous researches.   Potassium behaves much like sodium toward gaseous ammonia but the reaction is more rapid. On heating, colorless molten potassium amide acquires a faint greenish tinge which increases with the temperature.   There is no decomposition of this amide at 350°C.   At 400°C., it commences to volatilize.   At 500°C.. the distillation increases and the amide darkens.   At a full red heat it distills rapidly but decomposes only slowly into its elements.   In fact, potassium amide is so stable that, at a full red heat, it may be distilled in a current of hydrogen (hydride formed ?).   It condenses as a bluish-green liquid or a fine white sublimate.   Crystalline potassium amide has the same waxy appearance as sodium amide, but it is softer and less brittle (96).

The specific conductivity of potassium amide at 340°C. (nickel electrodes) is 0.389 mho and the decomposition voltage is 0.870 volt (104).

Rubidium amide

Investigations on rubidium amide have not been numerous (50, 84, 98).   Metallic rubidium is more reactive toward gaseous ammonia at all temperatures than is either sodium or potassium. The molten amide solidifies to a white, crystalline, glistening mass of small plates similar to potassium amide.   Rubidium amide has a tendency to creep when fused and distills unchanged above 400°C.

Cesium amide

Cesium amide has been prepared by Rengade (83).   When made in liquid ammonia, the amide may be made to crystallize

from this solvent in small prisms or plates. Rengade found the reaction between ammonia and cesium to be very rapid at a temperature slightly above the melting point of the amide (260°C.).

Mixtures of the alkali amides

Kraus and Cuy (70) have studied the system, potassium amide–sodium amide. The melting point diagram shows the existence of a compound $NaNH_2 \cdot 2KNH_2$ (transition point 120°C.), which is largely dissociated in the melt, and a eutectic mixture, containing 33 mole per cent of potassium amide and melting between 92 and 97°C. Such a mixture of these amides should prove very useful for low temperature fusions which are particularly desirable in some organic work.

Franklin (50) found that rubidium and potassium amides form isomorphous mixtures when crystallized from ammonia solution. "It is interesting to note that the crystals are obtained relatively richer in rubidium than the solution from which they are deposited. In one experiment recrystallization repeated three times gave a preparation which was nearly pure rubidium amide from a solution containing relatively a large quantity of potassium amide."

VI. DETERIORATION OF THE AMIDES DURING STORAGE

When using the alkali amides it is imperative that they be freshly prepared and preserved out of contact with the air. These substances are not only intensely hygroscopic but they are also very susceptible to oxidation. Numerous investigators have commented on the above properties of the amides. The observations of these men will be considered in the order of publication of their results. Drechsel (28) first showed that sodium nitrite is present in sodium amide which has been in contact with the air. De-Forcrand (25) states that on exposure to air sodium amide absorbs water, oxygen, and carbon dioxide and is converted into a mixture of sodium hydroxide, sodium nitrite, and sodium carbonate (cf. 62a; Part II, ref. 64, and ref. 171, p. 384). Winter (102) found sodium nitrite and traces of sodium hyponitrite in

sodium amide that had become yellow through exposure to air. Cesium amide is likewise readily oxidized with formation of cesium nitrite, cesium hydroxide, and ammonia according to Rengade (83; cf. 84). Muthmann (80) noted that sodium amide is gradually oxidized by the oxygen of the air, forming explosive mixtures which detonate apparently without external cause. He even measured the reaction velocity between oxygen and amide at different temperatures. Schrader (89) obtained a yellowish-red oxidation product on the exposure of finely divided sodium amide to air in the presence of a little moisture. He thought that this substance was a peroxide, probably of the formula, $NaNH_2 \cdot O_2$. He states that in dry air autoxidation does not take place at the ordinary temperature, but at $100°C$. to $110°C$. the peroxide is slowly formed. The most accurate work on the oxidation of the amides is that of Kraus and Whyte (72), who found that potassium amide in liquid ammonia solution is completely oxidized to potassium nitrite and potassium hydroxide by gaseous oxygen.

$$4KNH_2 + 3O_2 = 2KOH + 2KNO_2 + 2NH_3$$

Browne and Wilcoxon (16) in another connection observed that the addition of sodium nitrite to fused sodium amide resulted in immediate evolution of gas followed by a violent detonation. Even heating solid potassium amide and solid potassium nitrite *in vacuo* results in a vigorous explosion which shatters the containing vessel (32; cf. 62a).

This mass of observations shows that the alkali amides are rapidly acted upon by oxygen, carbon dioxide, and moisture of the air to give mixtures which are not only dangerously explosive but also contain a sufficient number of impurities to render them useless for many purposes. When a slight amount of contamination is not harmful, the amides may be preserved in bottles fitted with well greased glass stoppers. Even here, however, the amide deteriorates in time, losing much of its activity and becoming dangerous in that it may explode on heating. The best practice and the only one possible when a pure amide is desired is either to generate the amide in the vessel in which the desired fusion is

to take place, or to keep the amide always in an atmosphere of ammonia or of an inert gas.   Following the latter practice it is advisable to seal in each container, i.e., glass tube or bottle, a sufficient quantity of the amide for one experiment or, at least, to use all of the amide shortly after opening the container.   There is no observation on record which would indicate that the pure amides are in any way explosive or even unstable compounds. They become dangerous only when mixed with their oxidation products.   An examination of the literature shows that in many, if not in most, cases of laboratory accident an impure amide was used for investigation.   Such a procedure not only influences the yield of product but conceivably may even change the entire course of a reaction.

VII. ANALYSIS OF THE AMIDES AND OF THEIR REACTION PRODUCTS

Different methods of analysis have been used to demonstrate the composition of the amides.   Gay-Lussac and Thénard (58) arrived at the formulas of potassium and sodium amides by measuring the amount of ammonia absorbed and the amount of hydrogen evolved in their formation.   These investigators stressed the fact that the amount of hydrogen evolved on treating potassium with ammonia is the same as that which is evolved in the reaction of the same amount of potassium with water.   Davy (23) determined the gain in weight of potassium on being converted to the amide.   Beilstein and Geuther (2) determined the ratio of nitrogen to sodium by dissolving sodium amide in hydrochloric acid solution, determining the total solids formed, and then noting the loss of weight on ignition of the solid chlorides. Baumert and Landolt (1) analyzed potassium amide by observing both the gain in weight of potassium when ammonia is passed over it and the ratio of potassium chloride to ammonium chloride on dissolving the amide in hydrochloric acid solution.   Titherley (96) made a thorough study of the composition of sodium amide by synthetic means.   He determined first the weight of sodium amide formed from a given weight of sodium (repeated later by Miles (78)) and, second, the ratio between this increase in weight and the weight of hydrogen evolved.   He further deter-

mined the gain in weight when potassium, lithium, and rubidium (98) are converted into the amides. In the case of lithium amide, Titherley added a known weight of this substance to water, distilled off the ammonia into standard acid, titrated the lithium hydroxide remaining behind, and, finally, determined the lithium as sulfate. This last scheme of analysis is the one used and recommended by Dennis and Browne (26) for sodium amide and used since by Wöhler and Stang-Lund (104) and McGee (76). In the case of cesium amide, Rengade (83) noted only the amount of hydrogen evolved from a given weight of cesium. All the evidence available is consistent with the formula, MNH_2, for the alkali amides.

Winter (102), when working with sodium amide, was interested solely in the gases evolved on hydrolysis and determined them simply by placing the amide under water and collecting the gases by displacement of water in an inverted calibrated tube. In Miles' studies (78) concerning the action of hydrogen on sodium amide, he found a good agreement between the hydrogen evolved when the melt is treated with water and that calculated from the loss in weight of the amide during its reaction with hydrogen.

When studying the action of the fused amides upon various substances, the almost invariable practice has been to hydrolyze the melt and then examine the products of hydrolysis. Such a technique is open to serious objections because many of the amide fusion products are entirely destroyed or greatly altered by water. By carrying on fusions in such a way that the cold melt could be extracted with liquid ammonia, Fernelius and Bergstrom (31) were able to isolate in a pure state many of the products of amide fusions and to subject these products to direct analysis. The apparatus of these investigators also permitted them to observe visually the course of the reactions.

VIII. THE NATURE OF THE FUSED AMIDES

In view of suggestions in the literature that, in the reactions of sodium amide, the group NaNH— acts as a unit (97) and that potassium amide undergoes an acidic dissociation,

$$KNH_2 \rightleftharpoons KNH^- + H^+ \quad (94)$$

it is advisable to point out what is known concerning the ionic species present in the fused amides. Wöhler and Stang-Lund (104) proved the existence of amide ion, NH_2^-, and of sodium or potassium ion in the respective fused amides and found no evidence for the presence of any other ion. In this respect the alkali amides resemble the alkali hydroxides. By measuring the amount of electricity passed through the melt and by analyzing the anode gases, these investigators showed the validity of the equation,

$$6NH_2^- + 6 \ominus = 4NH_3 + N_2$$
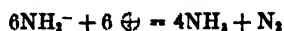
for the decomposition of the anion. At 210°C. with a low current density no trace of gas was generated at the cathode, although at a higher temperature and with greater current densities, the diffusion of the alkali metal (liberated at the cathode) into the anode region was sufficient to necessitate a correction for the ammonia used up and the hydrogen liberated by the reaction.

$$2Na + 2NH_3 = 2NaNH_2 + H_2$$
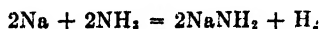
Electrolysis and migration experiments on solutions of the alkali amides in liquid ammonia indicate the presence of metal cations and amide anions (68).

IX. REACTIONS OF THE ELEMENTS WITH THE ALKALI AMIDES

The reactions of the alkali amides on the elements given below are grouped according to the Mendeléeff classification. These reactions are carried out in three ways: (1) in liquid ammonia solution; (2) in an inert solvent such as xylene, in which the amides are insoluble; and (3) in the fused amide. In general the three methods yield the same results, except that with the fused amides complications frequently arise, owing to the instability of the reaction products at the temperature of the melt. Unless otherwise noted, the reactions of the fused amides are those of Fernelius and Bergstrom (31).

Group I, Subgroup A

Hydrogen. Miles (78) found that sodium amide was partially converted into sodium hydride in a stream of hydrogen between 200°C. and 300°C.

$$NaNH_2 + H_2 = NaH + NH_3$$
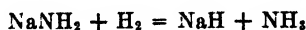
Titherley (96) did not find this reaction to take place when sodium amide is heated with hydrogen in an enclosed space up to 300°C. Guntz and Benoit (60) have shown the above reaction to be reversible in a stream of ammonia. They state that pure sodium hydride cannot be prepared by the action of hydrogen on sodium amide because with more than 33 per cent hydride, the melt becomes pasty and creeps along the walls of the vessel. Ruff and Geisel (85) several years before showed that the alkali hydrides react with liquid ammonia, yielding hydrogen and metal amides.

Dafert and Miklauz (21) reported a compound, trilithium ammonium, Li_3NH_4, which they obtained by heating (at 220–250°C.) lithium nitride in a current of hydrogen. In repeating this work Ruff and Goerges (86) showed this substance to be a mixture, or possibly a solid solution, of lithium amide (1 mole) and lithium hydride (2 moles).

$$Li_3N + 2H_2 = LiNH_2 + 2LiH$$
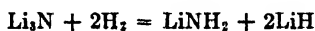
On heating this mixture at 340–480°C., the amide is converted into imide and ammonia, and the latter immediately combines with the hydride, forming lithium imide and hydrogen. Hence the total reaction is given by the equation.

$$2LiNH_2 + 4LiH = 2Li_2NH + 2LiH + 2H_2$$
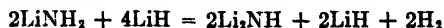
These investigators support their contention by the known decomposition of lithium amide into lithium imide at 240–450°C. and by the fact that at a slightly higher temperature lithium hydride reacts with ammonia with the formation of lithium amide.

Alkali metals. The alkali metals are, so far as has been observed, without action upon their amides. A small amount of

the metal seems to dissolve in the fused amide, forming a true solution (see above).

Group I, Subgroup B

Copper. Fused sodium amide does not act upon copper (29), while heated lithium nitride rapidly attacks this metal (21).

Silver. The resistance of silver to the fused amides has already been discussed. It seems justifiable to conclude that silver is relatively unattacked by these substances.

Gold. Fused sodium amide is without action on a gold crucible (51).

Group II, Subgroup B

Beryllium. Beryllium is dissolved slowly by fused sodium amide, with the production of sodium ammonoberylliate. Bergstrom (10) has prepared both sodium and potassium ammonoberylliates by the action of the respective amides on metallic beryllium in liquid ammonia.

$$Be + KNH_2 + 2NH_3 = Be(NH_2)NHK \cdot NH_3 + H_2$$
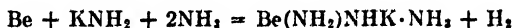
The mechanism of this reaction will be discussed in connection with a related reaction of magnesium.

Magnesium. Ephraim (29) examined the reaction between magnesium and sodium amide. He found that ammonia, hydrogen, and nitrogen are evolved, and that the reaction product, when an excess of magnesium was used, gives off ammonia in contact with water, which led him to assume that magnesium nitride, Mg_3N_2, was formed. He also says that his results point to the formation of free sodium because of the production of hydrogen, but he does not say that he showed the presence of this metal in the melt.

The senior author (3, 4, 6, 8, 9, 10) in a series of investigations has examined the reactions of sodium and potassium amides with numerous elements in liquid ammonia. Sodium amide and magnesium in this solvent react to give sodium ammonomagnesiate, in the following stepwise manner.

Magnesium first dissolves to a slight extent in ammonia to give magnesium ions, Mg^{++}, and solvated electrons, e^-,

$$Mg \rightleftarrows Mg^{++} + 2e^-$$

and sodium amide dissolves to give sodium and amide ions.

$$NaNH_2 \rightleftarrows Na^+ + NH_2^-$$

Since magnesium amide, $Mg(NH_2)_2$, is the least soluble of the various substances capable of formation from the four available ions, the following equilibrium lies far to the right.

$$Mg + 2NaNH_2 \rightleftarrows Mg(NH_2)_2 + 2Na$$
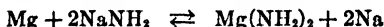
That metallic sodium is liberated is evidenced by the fact that (1) the solution becomes opaque blue in color, and (2) the sodium may be extracted from the solution by means of mercury. Liquid ammonia solutions of sodium are not particularly stable, however, especially in the presence of a metal which acts as a catalyst for the conversion of sodium into amide.

$$2Na + 2NH_3 = 2NaNH_2 + H_2$$
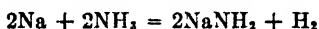
Furthermore, magnesium amide is an amphoteric substance which reacts with sodium amide to form the salt, sodium ammono-magnesiate.

$$Mg(NH_2)_2 + 2NaNH_2 = Mg(NHNa)_2 \cdot 2NH_3$$
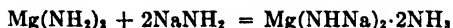
In this manner the equilibrium between sodium amide and magnesium is continually shifted to the right-hand side until one of these substances has reacted completely.

The course of the reaction between fused sodium amide and magnesium is essentially the same as that in ammonia solution. Immediately upon adding magnesium to the amide, globules of sodium form and float about on the surface of the melt. A white precipitate, visible through the clear melt and repeatedly observed, indicates the presence of magnesium amide. On continuing the fusion in an atmosphere of ammonia, the sodium is converted into amide and the melt becomes clear. The sodium ammonomagnesiate which is undoubtedly present cannot be

isolated because of the very low solubility of both the magnesiate and sodium amide in ammonia.

The course of the reaction between magnesium and potassium amide both in liquid ammonia (3) and in the fused state is identical with that for sodium amide described above. In the present instance, however, the soluble potassium amide can be extracted and the insoluble potassium ammonomagnesiate isolated in the pure state.

Zinc. Potassium ammonozincate, $Zn(NHK)_2 \cdot 2NH_3$, is formed by the action of the fused amide or its liquid ammonia solution (34) upon metallic zinc. The reaction is slow, however, and no blue color due to free potassium has been observed. Potassium amide in liquid ammonia solution readily attacks zinc amalgam (6), forming a mixture of zinc amide and potassium ammonozincate.

Cadmium. Fused potassium amide has little, if any, solvent action on cadmium. Likewise a liquid ammonia solution of potassium amide has no detectable action upon a cadmium rod over a period of months, although the same solution readily reacts with a liquid cadmium amalgam (6), forming a mixture of cadmium amide and potassium ammonocadmiate.

Mercury. Wöhler and Stang-Lund (104) report that mercury alone has no action upon molten sodium amide. When mercury is heated in contact with potassium amide for some time a dilute potassium amalgam results from the very slow decomposition of the amide into its elements.

Group II, Subgroup A

Calcium. Metallic calcium reacts with fused potassium amide to give potassium ammonocalciate, $CaNK \cdot 2NH_3$ and hydrogen.

Group III, Subgroup B

Boron. Boron appears to be slightly atacked by potassium amide although the reaction product has not been established.

Aluminum. Sodium and potassium amides in liquid ammonia react with aluminum (3, 4) after the fashion mentioned above for magnesium, to produce the very soluble aluminates. Aluminum

is readily attacked by sodium and potassium amides in the fused condition.   In the latter case an impure aluminum nitride was obtained by extracting the melt with liquid ammonia.

Thallium.   Metallic thallium is unattacked by fused potassium amide over a space of four and one-half hours.   A moderately strong solution of potassium amide in liquid ammonia has but very slight action on lump thallium over a period of eight months (6).

Rare earths

Cerium.   It seems not unlikely that a potassium ammono-cerite or an impure cerous nitride is formed by the reaction of fused potassium amide on metallic cerium.   A solution of potassium amide in liquid ammonia attacks cerium with the formation of potassium ammonocerite, $Ce(NHK)_3 \cdot 3NH_3$ (6).

Group IV, Subgroup A

Titanium and *zirconium* are attacked only very slightly, if at all, by fused potassium amide.

Thorium is but slightly attacked by fused potassium amide over a period of a few hours.   The reaction product has not been obtained in sufficient amount for identification.

Group IV, Subgroup B

Carbon.   One of the first references to the action of alkali amides upon carbon is that of Titherley (96), who says, "It is interesting to note that when complex organic matter is charred by the amides, sodium or potassium cyanide is found amongst the products of the decomposition."   At about this same time patents for the production of cyanides by the interaction of carbon and the alkali amides were issued (115, 116).   Szarvasy (95) and Dennis and Browne (26) have both mentioned that an iron retort introduces cyanides into sodium amide because of the carbon contained in the iron.   At about 500–600°C., carbon in the form of charcoal or coal reacts with sodium amide to form disodium cyanamide and hydrogen.

$$2NaNH_2 + C = Na_2NCN + 2H_2$$

Near 800°C., the cyanamide reacts with the excess of carbon to form cyanide.

$$Na_2NCN + C = 2NaCN$$

These reactions seem to depend upon temperature, because hydrogen and cyanamide are formed when sodium cyanide is dissolved in fused sodium amide at 400°C.

$$NaCN + NaNH_2 = Na_2NCN + H_2 \text{ (116)}$$

Silicon. Silicon is slightly attacked by fused potassium amide, probably with the formation of a potassium ammonosilicate.

Germanium. Finely divided metallic germanium reacts readily with fused potassium amide to liberate hydrogen and form a mixture of potassium ammonogermanate, KHNGeN, and potassium ammonogermanite, KNGe·NH$_2$.

$$Ge + KNH_2 + NH_3 = KHNGeN + 2H_2$$
$$Ge + KNH_2 + NH_3 = KNGe·NH_2 + H_2$$
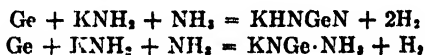
Germanium, in the form of either powder or lumps, is not appreciably attacked by a 0.6 N solution of potassium amide in two months (9).

Tin. Bergstrom has established the following equation as representing the reaction of dilute solutions of sodium and potassium amides upon tin in liquid ammonia.

$$10Sn + 6KNH_2 = 2SnNK·2NH_3 + K_4Sn_4$$

	Potassium ammonostannite	Potassium polystannide
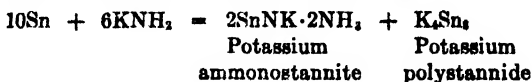
Although both the ammonostannites and the polystannides so formed are soluble in ammonia, the polystannides can be removed from solution by metallic mercury (9). This is an example of a very general type of reaction in which an element, electronegative or at least not strongly electropositive (amphoteric), reacts with a strong base to produce one compound, stannite, in which the element functions in an electropositive capacity, and another compound, polystannide, in which the element functions in an electronegative capacity. The reaction

is to be compared to the reaction of chlorine, or better, of sulfur, with potassium hydroxide.

$$Cl_2 + 2KOH \rightarrow KOCl + KCl + H_2O$$

$$3S + 6KOH \rightarrow K_2SO_3 + 2K_2S + 3H_2O$$

The reaction of sulfur is complicated somewhat by subsequent reactions of the products of the first reaction with more sulfur.

$$2(x + 1)S + 2K_2S \rightarrow 2K_2Sx$$

$$S + K_2SO_3 \rightarrow K_2S_2O_3 \text{ (cf. 117)}$$

Lead. Although sodium amide in liquid ammonia fails to react with lead, potassium amide reacts at times to give a green solution containing potassium polyplumbide, K_4Pb_9, and, presumably, potassium ammonoplumbite. Lead amalgam is not appreciably attacked by a solution of potassium amide (9).

Group V, Subgroup A

Tantalum is unattacked by fused potassium amide over a period of several hours.

Group V, Subgroup B

Nitrogen. Nitrogen is without action upon the fused amides (96).

Phosphorus. Winter (102) reports that, on warming, an energetic reaction occurs between sodium amide and yellow phosphorus with the production of sodium phosphide and other substances, including probably an amide of phosphorus. The water decomposition of his reaction product yielded hydrogen, phosphine, and ammonia. Winter was troubled because of the lack of a method for examining the substances obtained.

Both red and yellow phosphorus react readily with a liquid ammonia solution of potassium amide at room temperature to form a solution containing a polyphosphide of potassium and a light yellow precipitate, perhaps a potassium ammonophosphite. Sodium amide reacts in a similar manner with red phosphorus (9).

Arsenic. Arsenic reacts slowly with a solution of potassium

amide at room temperature with the production of red solutions indicative of the presence of complex anions containing arsenic. Sodium amide reacts slowly with arsenic in liquid ammonia (9).

Antimony. Antimony reacts with a liquid ammonia solution of potassium amide in the same manner that arsenic does. The reaction with sodium amide under similar conditions is very slow (9).

Bismuth. Potassium amide, and more particularly sodium amide, react with extreme slowness with bismuth in liquid ammonia (9).

Group VI, Subgroup A

Chromium gives no evidence of any reaction with a 0.5 N solution of potassium amide in liquid ammonia in four months (6) nor with molten potassium amide over a period of several hours.

Molybdenum. A moderately strong ammonia solution of potassium amide has only an extremely slight action upon lump molybdenum over a period of a year (6).

Tungsten. Lumps of tungsten are very slightly attacked by a moderately strong solution of potassium amide over a period of action of one year (6).

Uranium appears to be slightly attacked by fused potassium amide over a period of about three hours, but the product of the reaction has not been identified

Group VI, Subgroup B

Oxygen. The reaction of oxygen and the alkali amides has already been discussed; an alkali hydroxide and nitrite are obtained. The further reaction of the nitrite and excess amide to give nitrogen and hydroxide (see below),

$$KNO_2 + KNH_2 = 2KOH + N_2$$
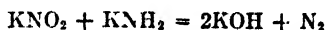
places the reaction of oxygen in a line with the reactions of the halogens and sulfur which also liberate nitrogen.

Sulfur. Ephraim (29) found that finely divided sodium amide suspended in xylene reacts with an excess of sulfur on heating to

give nitrogen, ammonia, sodium polysulfide, and apparently, in addition, a substance rich in nitrogen. The reactions of sodium amide with molten sulfur Ephraim found to be explosively violent. In liquid ammonia sulfur readily reacts with the alkali and alkaline earth amides to form polysulfides and soluble salts of unidentified ammono sulfur acids (9).

Selenium and *tellurium* react with liquid ammonia solutions of the alkali amides in essentially the same manner as sulfur. The products of the reactions are dependent upon the concentration of the reactants. The analysis of some of the ammono salts of selenium and tellurium is difficult because of their explosive character.

Group VII, Subgroup A

Manganese is only slightly attacked by fused sodium and potassium amides over a period of hours. The resulting compound is probably the hypomanganite which has been prepared by the slow reaction of potassium amide dissolved in liquid ammonia on lump manganese (4).

Group VII, Subgroup B

The halogens. Chlorine, bromine, and iodine all react vigorously with sodium amide to give sodium and ammonium halides and nitrogen (29). By modifying the conditions so that the reaction is not violent, it is possible to obtain nitrogenous halogen compounds such as chloramine or nitrogen chloride (104). The following equation represents the reaction of iodine with potassium amide in liquid ammonia at $-33°C$.

$$3I_2 + 6KNH_2 = 6KI + 4NH_3 + N_2 \text{ (9)}$$

Group VIII

Transition elements. The resistance of this group of elements to the fused amides has been discussed. None of them so far investigated is attacked to any great extent. The conversion of iron into ferric nitride, FeN, by means of heated barium nitride, Ba_3N_2, at once recalls to mind the related action of the metallic amides on the more electropositive elements (105).

Platinum appears to be slowly attacked by the molten amides (76). Iridium is unattacked by molten potassium amide over a period of fusion of four hours.

X. REACTIONS OF THE ALKALI AMIDES WITH COMPOUNDS

The reactions of salts with liquid ammonia solutions of the alkali amides have already been discussed. The reactions of compounds with the fused alkali amides follow in the main two courses: (1) the compound is reduced by the amide, or (2) the compound is ammonolyzed by the amide to form the corresponding compound of the ammonia system. The nature of the reducing action of the alkali amides has not been investigated. The most comprehensive investigation on this subject is that of Ephraim (29), and references unless otherwise noted are to his paper. It is to be borne in mind continually that the course of the reaction is judged by the products of hydrolysis of the fusion and not by the fusion products themselves.

Sulfur dioxide on warming with sodium amide reacts violently to give ammonia, hydrogen sulfide (ammonium sulfides?), and polysulfides (104); with potassium amide, sulfur dioxide reacts similarly giving amidosulfonic acids, ammonia, and other products (90).

Nitrous oxide bubbled into molten sodium amide gives sodium azide, ammonia, and sodium hydroxide (26, 63, 103, 104).

$$N_2O + 2NaNH_2 = NaN_3 + NH_3 + NaOH$$

This reaction serves as a starting point for the preparation of the azides.

Phosphorus pentoxide heated with sodium amide yields phosphine among other products (104). Carbon monoxide gives sodium cyanide when passed over heated sodium amide (2). Carbon dioxide, gives sodium cyanamide with some sodium carbonate and sodium cyanate (2, 27, 51, 66, 102). The factors which determine the relative amounts of these substances have not as yet been completely determined. Silica and boric oxide are supposed to react with sodium amide to give sodium silicate and sodium borate, respectively, together with the nitrides of

silicon and boron (96).   More likely mixed aquoammono-silicates and -borates are formed (81).   Aluminum, calcium, magnesium, and stannic oxides are not acted upon by sodium amide.   Cupric oxide, cadmium oxide, chromic anhydride, CrO_3, chromium trioxide, Cr_2O_3, ferric oxide, manganic oxide, and zinc oxide are all reduced, most of them to the metal.   Lead oxide on heating with sodium amide gives metal globules and a green black powder [polyplumbide (?)].   Mercuric oxide furnishes a sodium amalgam. Antimony and arsenic trioxides, Sb_2O_3 and As_2O_3, react to give sodium antimonite and sodium arsenite, respectively, together with some metal.   Likewise, tungsten trioxide, WO_3, and vanadium pentoxide, V_2O_5, react energetically to produce sodium tungstate and sodium vanadate, respectively.

Nitrosyl chloride reacts in the following manner when passed over warm potassium amide (96).

$$NOCl + 2KNH_2 = KCl + KOH + N_2 + NH_3$$
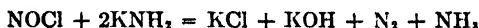
The reaction of carbon disulfide with sodium amide resembles that of carbon dioxide (2, 27), in that a mixed thioammonocarbonate, $NaSCN$, is formed.   Lead and copper sulfides and lead, sodium, and copper sulfates are all reduced by sodium amide. Bismuth sulfide gives a sodium–bismuth alloy on heating with sodium amide, while antimony sulfide gives sodium sulfantimonite, and arsenic sulfide gives arsine, arsenic, and sodium sulfarsenite.

The chlorides of lead, mercury, zinc, and barium are similarly reduced, while calcium and potassium chlorides are not acted upon by heated sodium amide.   The acid chlorides react very vigorously with sodium amide (96, 102).

Similarly phosphates, nitrates, and other oxygen salts of the heavy metals are reduced.   The hydroxides of these metals are dehydrated to the corresponding oxides.

Sodium nitrate and molten sodium amide give sodium azide (16),

$$NaNO_3 + 3NaNH_2 = NaN_3 + 3NaOH + NH_3$$

a simple ammonolysis, while sodium nitrite and sodium amide (also potassium nitrite and potassium amide; cf. 32) explode on

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heating. It seems likely from the analogous reaction of nitrosyl chloride above and from the reactions of certain organic derivatives of nitrous acid (33) that the reaction proceeds as follows:

$$KNO_2 + KNH_2 = 2KOH + N_2$$

This reaction can be interpreted likewise as a simple, though violent, ammonolysis—potassium aquonitrite is ammonolyzed by an ammono base to an aquo base and nitrous anammonide.

Glass. Titherley (96, 98) reports that the amides of lithium, sodium, potassium and rubidium all attack glass with the evolution of ammonia, but that the action of rubidium amide is not as marked as that of either sodium or potassium amide. Dennis and Browne (26) found that glass was clouded when heated in contact with fused sodium amide, but that it was not eaten away appreciably. McGee (76) used flint glass as a containing vessel for molten sodium amide and found that the cell became slightly etched after exposure to the fused amide for two or three days. Jena glass is likewise attacked to a slight extent by both sodium and potassium amides (104). It has been the experience of the authors that soda glass is attacked to a greater extent than the literature would lead one to believe, while Pyrex glass is fairly resistant but becomes etched within a few hours.

Porcelain. Titherley (96) reports that sodium amide does not attack porcelain very rapidly up to 300°C., but that the action increases considerably as the temperature is raised. Other investigators found that porcelain lost its glaze and assumed a dark brown color in contact with molten sodium amide (26). Fused lithium nitride (850°C.) rapidly attacks porcelain and other silicates. At 870°C. this nitride will eat through any containing vessel. It penetrates through vessels of magnesia as through a filter (21).

Silicates. Peterson (81) has been able to decompose finely ground silicate minerals sufficiently for a complete analysis by fusing them with sodium amide.

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PART II. ORGANIC REACTIONS

I. INTRODUCTION

In the first part of this article, a review was made of the prepa-
ration and properties of the alkali metal amides and of their
applications in the domain of inorganic chemistry.   In the second
part, the rather more extended field of the use of the metallic
amides in organic chemistry will be taken up, with the hope that
all types of reaction in which these amides play a part will be
mentioned.   Because of the limitations of space, it is inadvisable
to include a discussion of all of the compounds that have been
made with the use of these highly reactive ammono bases.

In reading the present article, it should be borne in mind that
many of the older investigators worked with sodium amide of
unknown or rather doubtful purity, Titherley (327), for example,
using material having a melting point 55°C. low, indicating the
presence of significant quantities of sodium hydroxide or sodium
oxide.   Guntz and Benoit (159) have recently shown that com-
mercial sodium amide—besides containing sodium hydroxide and
small quantities of iron—may be contaminated with as much as
11.75 per cent of sodium hydride, which could readily have been
eliminated by prolonged treatment with gaseous ammonia at
250-350°C.   Air oxidation of potassium and sodium amide
produces nitrites (311, 240, 270, 64), which may be converted by

heat into explosive nitrogen compounds—possibly mixed aquo-ammononitrites. Sodium amide is often made commercially (116, 151a) by passing ammonia through heated molten sodium to which there has been added a catalyst, such as sodium hydroxide or an oxide of one of the less electropositive metals. The influence of these impurities upon the course of the reactions in which sodium amide is used is naturally a matter of conjecture. Nevertheless, it is probable that most of the reactions described in the following pages are due primarily to sodium amide itself.

II THE OXIDES OF CARBON AND CARBON DISULFIDE

According to Beilstein and Geuther (28) carbon monoxide attacks warm sodium amide vigorously, the amide melting and finally becoming solid again when the reaction is complete. Sodium cyanide is formed, together with water, the latter of course reacting with unused sodium amide to form sodium hydroxide and ammonia. The reaction may be interpreted as the ammonolysis of a derivative of divalent carbon, carbon monoxide, to a salt of an ammonocarbonous acid, potassium cyanide (132).
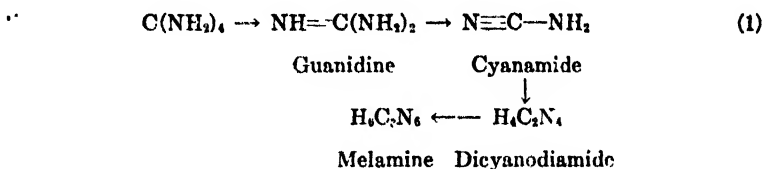
These authors have likewise found that carbon dioxide reacts vigorously with warm sodium amide to form disodium cyanamide, sodium hydroxide, and ammonia. A repetition of this work under more carefully controlled conditions has shown that sodium cyanate may be formed in this reaction as well as disodium cyanamide and sodium aquocarbonate (109a, 230). The first named salt appears to result from the action of carbon dioxide upon disodium cyanamide (230). Carbon dioxide is therefore ammonolyzed by sodium amide and converted to a sodium ammonocarbonate, disodium cyanamide, and then by the further action of carbon dioxide, to the sodium salt of a mixed aquo-ammonocarbonic acid, sodium cyanate (40). It should be noted that if sodium cyanate is the primary product of the above reaction between carbon dioxide and fused sodium amide in excess, it would soon be converted to cyanamide (127a, 109a) and therefore could not be detected.

Beilstein and Geuther (28) and Drechsel (109b) report that sodium thiocyanate, a mixed thioammonocarbonate, is found

among the products of the action of carbon disulfide on sodium amide.

III. AMMONOCARBONIC ACIDS (CYANAMIDE, GUANIDINE, ETC.)

Franklin (127) has shown that the progressive deammonation of the hypothetical ammonoorthocarbonic acid, $C(NH_3)_4$, leads to a series of ammonocarbonic acids, which include the known substances guanidine, biguanide, cyanamide, dicyanodiamide, melamine, and the less well-known melam, melem, and hydromelonic acid.

$$C(NH_3)_4 \rightarrow NH=C(NH_3)_2 \rightarrow N\equiv C-NH_3 \qquad (1)$$

$$\text{Guanidine} \qquad \qquad \text{Cyanamide}$$

$$\downarrow$$

$$H_6C_3N_6 \longleftarrow H_4C_2N_4$$

$$\text{Melamine} \quad \text{Dicyanodiamide}$$

While a detailed review of this interesting class of substances is outside the scope of the present article, it may be pointed out that Franklin was able to prepare salts of all of the definitely known ammonocarbonic acids by treating them in liquid ammonia solution with the ammono base, potassium amide. Thus, dipotassium guanidine is formed as a precipitate when guanidine nitrate is added to an excess of a solution of potassium, the reaction proceeding in accordance with the equation

$$H_6CN_3 \cdot HNO_3 + 3KNH_2 = K_2H_3CN_3 + KNO_3 + 3NH_3 \qquad (2)$$
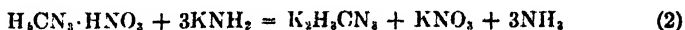
Guanidine nitrate, rather than guanidine itself, is used in this reaction because the latter substance is very hygroscopic. Disodium triphenylguanidine is formed as a readily soluble salt by the action of the sparingly soluble sodium amide upon a liquid ammonia solution of triphenylguanidine, a triphenyl acid ester of an ammonocarbonic acid.

$$(C_6H_5)_3CN_3H_2 + 2NaNH_2 = (C_6H_5)_3CN_3Na_2 + 2NH_3 \qquad (3)$$
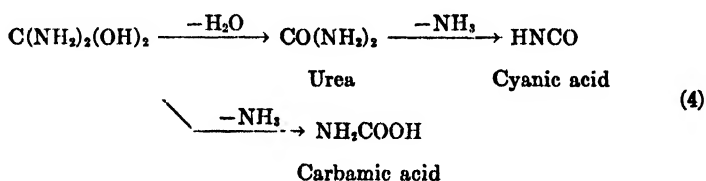
Franklin furthermore makes the interesting observation that disodium cyanamide is the only ammonocarbonic acid formed when any of the other ammonocarbonic acids, or for that matter

any of the aquocarbonates, carbon dioxide or the mixed aquo-ammonocarbonic acids of the type of urea are fused with an excess of sodium amide or potassium amide.

IV. MIXED AQUOAMMONOCARBONIC ACIDS

Blair (40, 41) has pointed out the existence of a class of substances which may be regarded as carbonic acids related to the water and ammonia systems at the same time, and which may therefore logically be termed mixed aquoammonocarbonic acids. Thus, the hypothetical mixed aquoammonoorthocarbonic acid, $C(NH_2)_2(OH)_2$, may lose water or ammonia, in the manner of the scheme below, to give the mixed type acids, urea, carbamic acid, and cyanic acid.

$$C(NH_2)_2(OH)_2 \xrightarrow{\ -H_2O\ } CO(NH_2)_2 \xrightarrow{\ -NH_3\ } HNCO$$

$$\text{Urea} \qquad\qquad \text{Cyanic acid}$$

$$\xrightarrow[\qquad]{-NH_3} NH_2COOH \tag{4}$$

$$\text{Carbamic acid}$$

Blair has verified the earlier work of Franklin and Stafford (136) and has prepared the mono- and di-potassium salts of urea by the action of potassium amide upon a liquid ammonia solution of urea, in accordance with the equation

$$CO(NH_2)_2 + KNH_2 = CO(NH_2)(NHK) + NH_3 \tag{5}$$
$$CO(NH_2)NHK + KNH_2 = CO(NHK)_2 + NH_3$$
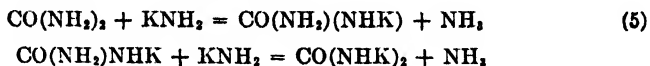
The symmetrical structure of the dipotassium salt has not been proven. Blair has similarly prepared the potassium salts of carbamic acid, biuret, and allophanic acid. It is perhaps needless to mention that many of these salts are incapable of existence in water solution.

V. HYDROCARBONS

A. Saturated and unsaturated (ethylenic) hydrocarbons

In accordance with our expectations, the saturated paraffin hydrocarbons exhibit no acid properties whatsoever in liquid

ammonia towards the bases, sodium amide and potassium amide. At more elevated temperatures, in the neighborhood of the melting points of the amides, the paraffin hydrocarbons containing several atoms of carbon are cracked to lower hydrocarbons and hydrogen, with the simultaneous formation of some dipotassium cyanamide (146).

The effect of sodium amide upon ethylenic hydrocarbons does not appear to have been investigated. The senior author has made the observation (34) that dipentene, a mixture of trimethylethylene and sym-methylethylethylene, pentene-2, cyclohexene, stilbene, and styrene react with potassium amide in liquid ammonia at room temperatures to form red or reddish-brown solutions. The reactions, which are far from complete with all of the above named compounds except stilbene and styrene, may indicate salt formation in which a hydrogen atom of the hydrocarbon is replaced by potassium, or they may indicate that potassium amide has added to the ethylenic double bond. Muskat (269) has found that potassium amide, dissolved in liquid ammonia, adds to one of the double bonds of 1-phenylbutadiene, forming an addition compound which is converted to an unsaturated amine by hydrolysis.

B. Acetylenic and aromatic hydrocarbons

Acetylene itself, and all true acetylenic hydrocarbons that contain a free methine group, $\equiv$CH, react with sodium amide in liquid ammonia to form salts of the composition, $R \cdot C \equiv C \cdot Na$, in theoretical yield (281; cf. 251). The sodium derivatives of some of the higher true acetylenes may conveniently be made in boiling benzene, as Picon has found, but it is stated that the lower homologues fail to react with sodium amide under these conditions. A few years later, Bourguel (71b, 56a) came to the conclusion that Picon's failure to prepare the sodium derivatives of acetylenic hydrocarbons in cold ether or benzene was due to the alteration of the surface of the amide by the action of moist air. Sodium amide, ground to a fine powder under vaseline oil or other suitable inert liquid, and suspended in ether, reacts readily with all true acetylenes (that is, with hydrocarbons containing a free

methine group) at room temperatures with only a slight evolution of heat (56a, 58). Both Picon and Bourguel recommend the use of sodium amide for the preparation of the sodium salts of the true acetylenes, since the reaction is more rapid and complete than when metallic sodium is used for the purpose, and the possibility of the formation of reduction products is eliminated (cf. 245). Meunier and Desparmet (261) have prepared the sodium salts of a number of acetylenic hydrocarbons without the use of a solvent.

Disubstituted acetylenes of the type, $R \cdot C \equiv C \cdot CH_3$, $R \cdot C \equiv C \cdot C_2H_5$, etc., are transformed by sodium amide into a true acetylene, in accordance with the equations

$$R \cdot C \equiv C \cdot CH_3 + NaNH_2 = R \cdot CH_2 C \equiv C \cdot Na + NH_3 \qquad (6a)$$

$$R \cdot C \equiv C \cdot C_2H_5 + NaNH_2 = R \cdot CH_2 CH_2 C \equiv C \cdot Na + NH_3 \qquad (6b)$$

$$R' \cdot C \equiv C \cdot Na + (ice)\ H_2O = R'C \equiv CH + NaOH \qquad (6c)$$

These transpositions best take place when one mole of the disubstituted acetylene is heated to 150–160°C. with 1.2 equivalents of sodium amide under vaseline or paraffin oil. The isomerization is not always complete. In order to isolate the reaction product, the vaseline oil, together with any unchanged disubstituted acetylene, is distilled from the solid, which consists of the sodium salt of the desired hydrocarbon. The hydrocarbon itself is obtained by hydrolysis of its salt (see equation 6c) (59). The rearrangement expressed in equations 6a and 6b was first observed by Favorsky (117), who heated a disubstituted acetylene with metallic sodium in a sealed tube.

A few years later, Bourguel (72) reinvestigated this reaction in an attempt to elucidate its mechanism. He found that sodium amide, even at 60–70°C., slowly isomerizes methylphenylacetylene, $C_6H_5C \equiv CCH_3$, to phenylpropine, $C_6H_5CH_2C \equiv CH$, and a new hydrocarbon, believed to be $C_6H_5CH = C = CH_2$. This latter, on further treatment with sodium amide, is changed to phenylpropine.

Lebeau and Picon (244; cf. 251) prepared a few monoalkylated acetylenes in satisfactory yield by the action of the lower alkyl iodides on monosodium acetylene in liquid ammonia at tempera-

tures ranging from $-50°C.$ to $-30°C.$, depending upon the nature of R in the equation

$$CH\equiv C\cdot Na + RI = NaI + CH\equiv C\cdot R \qquad (7)$$
$$R = CH_3, n\text{-}C_4H_9, \text{ etc.}$$
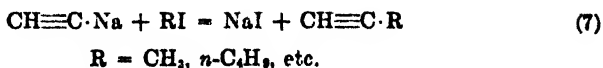
In continuation of this work, Picon (278a, 280) carried out the reaction of equation 7 in an autoclave at room temperatures, likewise using liquid ammonia as the solvent. Homologous acetylenes were in this manner prepared from monosodium acetylene and the primary alkyl iodides, n-heptine and n-decine thus being obtained in yields of 40 and 65 per cent of the theoretical, respectively. A little platinum black often acts favorably as a catalyst.

Alkyl iodides with a branched chain either on the carbon carrying the halogen, or on the adjacent carbon, are converted by monosodium acetylene in ammonia to the corresponding ethylenic hydrocarbon, with elimination of hydrogen iodide.

$$CH\equiv C\cdot Na + R\cdot CHR'\cdot CH_2I = CH\equiv CH + RR'C=CH_2 + NaI \qquad (8)$$

As illustrations of this reaction, isopropyl and sec-hexyl iodides, submitted to the process of equation 8, were converted to propylene and hexylene in yields of 83 and 79 per cent, respectively.

A possible, although untested, explanation of the formation of ethylenic hydrocarbons in this reaction may be advanced by assuming that monosodium acetylene is slightly ammonolyzed in liquid ammonia to acetylene and sodium amide. (Acetylene is slightly soluble in ammonia.) The latter base is known from the work of Chablay (79) to react with primary alkyl halides in liquid ammonia to form unsaturated hydrocarbons. Presumably, secondary halides of the type of isopropyl iodide would be changed to olefin even by the very low concentration of sodium amide in equilibrium with a solution of monosodium acetylene.

Bourguel (61), at a later date, found that dimethyl sulfate reacts rapidly with monosodium acetylene under ether at ordinary temperatures in accordance with the equation

$$R\cdot C\equiv C\cdot Na + (CH_3)_2SO_4 = R\cdot C\equiv C\cdot CH_3 + Na(CH_3)SO_4 \qquad (9)$$

Monosodium acetylene readily absorbs carbon dioxide, either in the presence or absence of a solvent, such as benzene, to form the salt of an acetylenic acid (56b, 261, 60).

$$R \cdot C \equiv C \cdot Na + CO_2 = R \cdot C \equiv C \cdot COONa \qquad (10)$$

Bourguel (60) has described an interesting method for increasing the length of the carbon chain of an acetylenic hydrocarbon. A monosubstituted acetylene, $R \cdot C \equiv CH$, is converted to its sodium salt and then methylated, in accordance with equation 9. The resulting disubstituted acetylene, $R \cdot C \equiv C \cdot CH_3$, is isomerized by sodium amide to $R \cdot CH_2 C \equiv C \cdot Na$ (equation 6a), this is again methylated, and the process repeated until the desired product is synthesized. The yield in each step is about 80 per cent of the theory. Thus from 500 grams of cyclohexylpropine, $C_6H_{11}CH_2C \equiv CH$, there was obtained 200 grams of cyclohexylhexine, $C_6H_{11}(CH_2)_4C \equiv CH$, by the method just described.
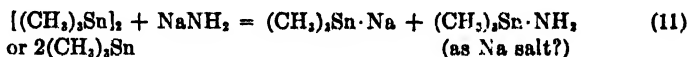
The foregoing section has dealt with the direct replacement of the hydrogen atom of a methine group by sodium. The observation has been made by Grignard and Lapyre (157) that a methylene group, activated by the influence of a triple and a double bond (and presumably also by the influence of two triple bonds), reacts with sodium amide with the evolution of ammonia, indicating the formation of a sodium salt. Thus, ammonia in slight excess of one mole is given off when 1-phenylpentene-4-ine-1, $C_6H_5C \equiv C-CH_2-CH=CH_2$, is heated with sodium amide in boiling toluene, suggesting the partial rearrangement of the hydrocarbon to a true acetylene (cf. equations 6a and 6b).

The activation of a methane hydrogen atom by phenyl groups attached to the same carbon atom has been known for a number of years. Kraus and Rosen (239) were the first to observe that potassium amide, in liquid ammonia solution, reacts with triphenylmethane to form a potassium salt of the composition, $(C_6H_5)_3C \cdot K$. As this salt dissolves readily in ammonia with an intense red color which may be discharged by acids (such as ammonium salts, etc.), it may be used as an indicator.

Wooster and Mitchell (351) and later Wooster and Ryan (352) in extending the observations of Kraus and Rosen, have shown

that hydrocarbons containing a benzohydryl group, $(C_6H_5)_2CH—$, react with potassium amide (or with metallic sodium) to form red colored salts of the type of potassium triphenylmethyl. Thus, diphenylmethane, triphenylmethane, diphenylbenzylmethane, and *sym*-tetraphenylethane so react, but toluene, ethylbenzene, tetraphenylmethane, etc., fail to react because they do not contain the benzohydryl group.

Hexaphenylethane is reported by Wooster and Mitchell (351) to add potassium amide in liquid ammonia solution. No experiments are described. Supposedly, this addition is similar to the reaction between sodium amide and hexamethylstannoethane in liquid ammonia (238), which is known to follow the scheme

$$[(CH_3)_3Sn]_2 + NaNH_2 = (CH_3)_3Sn·Na + (CH_3)_3Sn·NH_2 \qquad (11)$$
$$\text{or } 2(CH_3)_3Sn \qquad\qquad\qquad (\text{as Na salt?})$$

Aside from the fact that chlorine is not measurably dissociated under ordinary conditions into atoms, this reaction is analogous to the conversion of chlorine into sodium chloride and hypochlorite by cold aqueous sodium hydroxide, in accordance with the equation

$$Cl_2 + 2NaOH = NaCl + ClONa + H_2O \qquad (12)$$

Naphthalene is stated by Germuth (152) to be attacked by fused sodium amide at 215–220°C. with the formation of pure α-naphthylamine. No experiments are described. Sachs (300a) in an attempt to prepare aminophenols by fusing sodium amide with phenol in the presence of naphthalene, was surprised to obtain, instead of the expected products, α-naphthylamine and 1,5-naphthylenediamine. Hydrogen was evolved when the melt was hydrolyzed with water, possibly because of the presence of sodium hydride. This may have been formed, however, by the action of hydrogen upon the sodium amide (268a). Here, as in Germuth's experiments, an amino group is introduced into the aromatic nucleus, just as is a hydroxyl group in the well-known reaction between fused sodium hydroxide and phenol or resorcinol to form phloroglucinol (13). It will be noted that 1,5-naphthylenediamine is formed in the reaction of Sachs, in accordance with

the theory that the amino group will activate the ring of which it is a member for reactions with negative center-seeking reagents, such as nitric acid (the NO_2^+ of which is active in nitrations), but will deactivate it for reactions with positive center-seeking reagents, such as sodium amide or sodium hydroxide (the OH^- or NH_2^- in this case being active in substitution) (226).

Kraus and Neal (238) have observed that trimethylstannane, $(CH_3)_3SnH$, is converted to a sodium salt, $(CH_3)_3Sn \cdot Na$, by sodium amide in liquid ammonia. At the same time, hydrogen and trimethylstannylamine are formed in the peculiar reaction

$$2(CH_3)_3SnH + NaNH_2 = (CH_3)_3 Sn \cdot Na + (CH_3)_3SnNH_2 + H_2 \quad (13)$$
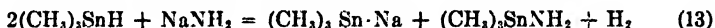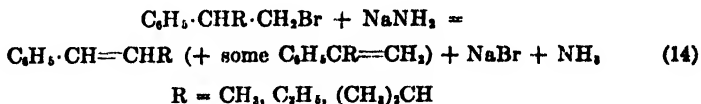
VI. HALOGEN COMPOUNDS

A. Paraffin monohalides

Shortly after the middle of the last century, Baumert and Landolt (25) examined the reaction between potassium amide and the ethyl halides, but without definite results. At a later date Titherley (328, 329) reported that sodium amide either does not react with ethyl iodide and ethylene dibromide in the absence of solvent, or, when change does occur at higher temperature, complete decomposition and charring takes place. Alexieff (5) reports that sodium amide reacts with amyl iodide in a sealed tube at 152°C. to form a mixture of the three amylamines, the tertiary predominating. Chablay (79), working under more regulated conditions, added alkyl halides gradually to suspensions of sodium amide in liquid ammonia at its normal boiling point. With methyl iodide, the reaction is very vigorous and is said to lead to the formation of methylamine, although it is known that some tetramethylammonium iodide is formed by the action of methyl iodide on liquid ammonia alone (345). The higher alkyl halides react with sodium amide to produce unsaturated hydrocarbons in amounts increasing with the molecular weight of the halide. Thus, ethylene is obtained in 5.4 per cent yield from ethyl iodide, propylene in 37 and 69.6 per cent yields from n-propyl iodide and n-propyl chloride, respectively, and isobutylene in 62.4 per cent yield from isobutyl iodide or in 83.6 per cent yield from isobutyl chloride.

Picon (279), finding that mixtures of primary, secondary, and tertiary ethylamines were formed by the action of liquid ammonia on the ethyl halides, attempted to prepare pure ethylamine by the action of sodium amide on ethyl chloride at 0°C. (autoclave). The low yield of ethylamine, 30 per cent of the theory, is due to the formation of considerable quantities of ethylene, partly, perhaps, because the heat liberated in the reaction warmed the contents of the autoclave to 50°C. Less satisfactory results were obtained with ethyl iodide or bromide, owing to the production of secondary and tertiary amines.

The reactions that have just been discussed consist (1) in the ammonolysis of ethyl chloride by a base of the ammonia system, sodium amide, to sodium chloride and an ammono alcohol, ethylamine, and (2) in the abstraction of hydrogen halide from the alkyl halide to form an unsaturated hydrocarbon, a reaction in which alcoholic potash is usually used in place of sodium amide.

Mlle. Amagat (6) has found that unsaturated hydrocarbons are formed when phenylalkylethyl bromides are heated with sodium amide in boiling xylene for five to six hours, in accordance with the general equation
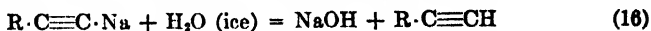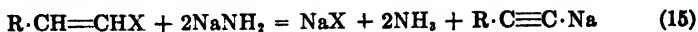
$$C_6H_5 \cdot CHR \cdot CH_2Br + NaNH_2 =$$
$$C_6H_5 \cdot CH{=}CHR \; (+ \text{ some } C_6H_5CR{=}CH_2) + NaBr + NH_3 \qquad (14)$$
$$R = CH_3, C_2H_5, (CH_3)_2CH$$

It will be noted that one of the groups has migrated during the reaction. The expected hydrocarbon, $C_6H_5CR{=}CH_2$, is obtained in very small amount. 1-Bromo-3-phenylpropane, $C_6H_5CH_2CH_2CH_2Br$, is not attacked by sodium amide under the conditions of the previous experiments, but in boiling diphenylmethane it is converted to a mixture of the corresponding secondary and tertiary amines.

B. Unsaturated monohalides

Bourguel and Lespieau (58, 67, 248), following earlier work of Meunier and Desparmet (260, 259), have obtained acetylenic hydrocarbons by treating halogen derivatives of ethylenic hydrocarbons with sodium amide in an inert liquid (toluene, xylene, but generally vaseline or paraffin oil boiling at or above 160°C.

(56c)) whose boiling point is governed by the difficulty with which the reaction occurs. The two equations below express in the main the course of the reactions.

$$R \cdot CH{=}CHX + 2NaNH_2 = NaX + 2NH_3 + R \cdot C{\equiv}C \cdot Na \qquad (15)$$

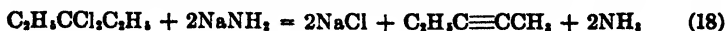$$R \cdot C{\equiv}C \cdot Na + H_2O \text{ (ice)} = NaOH + R \cdot C{\equiv}CH \qquad (16)$$

(X = a halogen, generally Cl or Br; R = an alkyl or hydroaromatic radical.)

Bourguel (68, 69), as the result of a series of investigations, has come to the conclusion that sodium amide is superior to sodium or potassium hydroxide for the preparation of acetylenic hydrocarbons by the abstraction of halogen acids from a paraffin dihalide, or from an ethylenic monohalide, in that polymerization and reduction are minimized, yields are increased, and the products are purer.

Since it is the purpose of this review to include, in an article of not too great a length, a discussion of all of the known types of reaction in which sodium amide plays a part, it has been found necessary to abbreviate some topics, such as the present one dealing with the synthesis of acetylenic hydrocarbons. Mention therefore can be made of only a few specific preparations.

(1) Lespieau and Bourguel (250) made cyclohexylpropine, $C_6H_{11}CH_2C{\equiv}CH$, in 66 per cent yield by heating cyclohexylbromopropene, $C_6H_{11}CH_2CBr{=}CH_2$, with 3 mole proportions of sodium amide in mineral oil at a temperature of 160–165°C. The reaction followed the type equation (15), and required three to four hours for completion. The authors emphasize the necessity for using a finely pulverized sodium amide, as free as possible from sodium hydroxide.

(2) By treatment with phosphorus pentachloride, diethyl ketone, $(C_2H_5)_2C{=}O$, was converted to a mixture of the chlorides, $C_2H_5CCl{=}CHCH_3$ and $(C_2H_5)_2CCl_2$, which were heated for five hours with sodium amide in boiling xylene (57a). The reaction was considered complete when the evolution of ammonia, formed in accordance with equations 17 to 19 below, had practically ceased.

$$C_2H_5CCl{=}CHCH_3 + NaNH_2 = C_2H_5C{\equiv}CCH_3 + NaCl + NH_3 \qquad (17)$$

$$C_2H_5CCl_2C_2H_5 + 2NaNH_2 = 2NaCl + C_2H_5C{\equiv}CCH_3 + 2NH_3 \qquad (18)$$

$$C_2H_5C{\equiv}CCH_3 + NaNH_2 = C_2H_5CH_2C{\equiv}CNa + NH_3 \qquad (19)$$

The contents of the reaction flask were distilled directly, to remove the paraffin oil and a small amount of pentine-2 (see equation 17) that escaped the rearrangement of equation 19. The main reaction product, pentine-1, $CH_3CH_2CH_2C{\equiv}CH$, was obtained in 30 per cent yield by hydrolyzing the solid remaining in the flask with ice and water (cf. equation 6c). It is thus seen that under the proper conditions, a true acetylenic hydrocarbon, $R{\cdot}C{\equiv}CH$, is generally the principal product of the abstraction of hydrogen halide from a paraffin dihalide, $RCCl_2R'$ or from an unsaturated monohalide, $RCCl{=}CH_2R'$ (R' equals an aliphatic radical), irrespective of the position of the halogen atoms in the molecule.

(3) In a similar fashion, 4-chloroheptene-3, $C_3H_7{\cdot}CCl{=}CH{\cdot}C_2H_5$, is converted by sodium amide in pseudocumene, at 140°C., into heptine-3, $C_3H_7C{\equiv}CC_2H_5$ and heptine-1, $CH_3(CH_2)_4C{\equiv}CH$, in yields of 40 and 15 per cent, respectively. The former compound may be converted into the latter, in the manner of equation 6b, by the long continued action of sodium amide at 170°C. It is especially to be noted that heptine-3 undergoes this transposition more slowly than do the acetylenic hydrocarbons with the triple bond in the 2-position (octine-2, nonine-2) (62). Better yields of the true acetylenic hydrocarbons, $R{\cdot}C{\equiv}CH$, have been obtained by Bourguel in other reactions of the type just discussed (66).

In accordance with equation 15, one might logically expect that the abstraction of hydrogen halide from a halogenated hydrocarbon $R{-}CX{=}CH_2$, followed by a subsequent reaction of the acetylenic hydrocarbon so formed with another molecule of sodium amide, would give a sodium salt of the composition, $R{\cdot}C{\equiv}C{\cdot}Na$. Peculiarly enough, Bourguel (63) found that the solid product of these reactions did not behave as a homogeneous substance, for it contained in addition to the salt, $R{\cdot}C{\equiv}C{\cdot}Na$, a substance whose properties are in agreement with one of the formulas,

$$R{\cdot}C{\equiv}CH{\cdot}NaNH_2 \quad or \quad R{\cdot}C{\equiv}CNH_2Na \qquad (20)$$

The second alternative structure is improbable, since the so-called "sodammonium," $NaNH_3$, to which it is related, does not exist

(235, 237, 287). Furthermore, a reasonable electronic structure cannot be assigned to it.

Leaving constitutional questions out of consideration for the present, it has been found that a portion of the solid resulting from the action of sodium amide on an unsaturated monohalide reacts with carbon dioxide and dimethyl sulfate to regenerate the parent acetylene, $R \cdot C \equiv CH$, while another part of the solid, consisting of the sodium salt, $R \cdot C \equiv C \cdot Na$, is converted to the expected products, $R \cdot C \equiv C \cdot COONa$ and $R \cdot C \equiv C \cdot CH_3$, in accordance with equations 9 and 10.

C. Paraffin polyhalides

Meunier and Desparmet (260; cf. 28) report that sodium amide reacts with chloroform and bromoform, in the absence of a solvent, to form sodium halide and sodium cyanide. The reaction, although slow to start, may become violent.

$$4NaNH_2 + CHCl_3 = NaCN + 3NaCl + 3NH_3 \qquad (21)$$
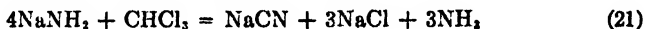
Since hydrocyanic acid may be regarded as a derivative of formic acid (cf. 132), the above reaction is related to the synthesis of orthoformic esters by the action of alkali alcoholates on chloroform.

A benzene solution of equimolecular amounts of chloroform and aniline, heated with three equivalents of sodium amide, gives phenyl isocyanide, in accordance with the equation

$$CHCl_3 + 3NaNH_2 + C_6H_5NH_2 = C_6H_5NC + 3NaCl + 3NH_3 \qquad (22)$$

The yields are not given. Muthmann (270) subsequently reports a qualitative verification of this reaction.

Meunier and Desparmet (259, 260) found that sodium amide reacts with ethylene dibromide at 100°C., in the absence of solvent, to form acetylene, sodium bromide, and ammonia. Titherley (328) previously examined this reaction without satisfactory results.

Bourguel (69) as well as Meunier and Desparmet (261) and Lespieau (247) prepared acetylenic hydrocarbons by treating 1,1- or 1,2-paraffin dihalides with sodium amide under an inert hydro-

carbon of high boiling point (toluene, xylene, paraffin oil, etc.). The equations which represent these reactions are generalized below.

$$R \cdot CHX \cdot CH_2X + 3NaNH_2 = R \cdot C \equiv C \cdot Na + 2NaBr + 3NH_3 \qquad (23)$$

$$R \cdot CX_2 \cdot CH_3 + 3NaNH_2 = R \cdot C \equiv C \cdot Na + 2NaBr + 3NH_3 \qquad (24)$$

$$R \cdot CH_2CHX_2 + 3NaNH_2 = R \cdot C \equiv C \cdot Na + 2NaBr + 3NH_3 \qquad (25)$$

The sodium salts of the acetylenic hydrocarbons may be converted by hydrolysis into the acetylenes themselves (equation 6c).

It will be remembered from the preceding section (B) that unsaturated monohalides of the type, $R \cdot CX = CHCH_3$, react with sodium amide at elevated temperatures to form the sodium salt of a true acetylene, $R \cdot CH_2C \equiv C \cdot Na$ (cf. equations 6a, 6b, 19). Similarly, true acetylenes. $R \cdot C \equiv CH$, are generally the chief products of the action of sodium amide under these conditions on any of the dihalides whose formulas are given in equations 23 to 25.

The reactions just discussed will be made more understandable by the consideration of a few concrete examples. Ethylbenzene, $C_6H_5C_2H_5$, is brominated to styrene dibromide, $C_6H_5 \cdot CHBr \cdot CH_2Br$, and this is slowly introduced into a mixture of sodium amide with a high-boiling petroleum fraction heated to about 160°C. The reaction is rapid, and is practically complete half an hour after the addition of the last of the dibromide. Distillation of the petroleum fraction from the solid residue yields a small quantity of styrene, $C_6H_5CH = CH_2$, which has been formed by the removal of two atoms of bromine from the styrene dibromide. Although metallic sodium would have caused this side reaction, it was not present in the sodium amide which Bourguel used in these experiments. The water-ice hydrolysis of the solid residue left after the distillation yields phenylacetylene in about 40 per cent of the theory (58a).

Because of the formation of ethylenic hydrocarbons in the reactions of equations 23 and 24, it is often profitable first to convert a ketone dihalide, $R \cdot CX_2 \cdot CH_2 \cdot R'$, to an unsaturated monohalide, $RCX = CHR'$ by the action of alcoholic potash, and
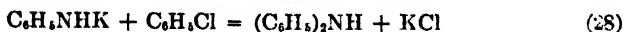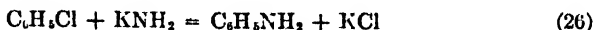
then by the action of sodium amide to an acetylenic hydrocarbon (equations 15, 17, 19).

Secondary octyl alcohol, $C_6H_{13} \cdot CHOH \cdot CH_3$, is dehydrated by zinc chloride to a mixture of octenes, in which the compound $C_5H_{11} \cdot CH=CH \cdot CH_3$ predominates. Bromine changes this to a dibromide, $C_5H_{11} \cdot CHBr \cdot CHBr \cdot CH_3$, from which there may be obtained octylene (40 per cent), octine-1, $C_6H_{13}C\equiv CH$ (25 per cent), and a mixture of octines-2 and -3 (8 per cent) (compare equations 17, 19). It is evident that the chief reaction product is an ethylenic hydrocarbon, formed by a parasitic reaction. To avoid this, it is best to start with a monobromoöctylene, of the composition, $C_5H_{11}CBr=CHCH_3$. The yield of octine-1 may thereby be increased (57).

Titherley (329) states that "carbon hexachloride" (hexachloro-ethane?) is decomposed by sodium amide to form a mixture of products which include sodium cyanide, chloride, and cyanamide. The reaction has not been carried out under regulated conditions.

D. Aromatic halides

Titherley (329) may be credited with the first qualitative observation to the effect that sodium amide slowly attacks chlorobenzene, ammonia and phenyl isocyanide being isolated from the rather complex reaction mixture. The latter compound may owe its origin to the presence of cyanide in the sodium amide used. Sachs (298), by "melting" chloro- or bromo-benzene with sodium amide, obtained aniline in poor yield. Gilkey (153), working in the laboratories of Stanford University, has shown that chloro- and bromo-benzene react vigorously with a liquid ammonia solution of potassium amide at $-33°C.$, a somewhat unexpected fact when one remembers the inertness of the halogeno benzenes toward cold aqueous alkali. By adding chlorobenzene to three equivalents of potassium amide in ammonia, Gilkey obtained 50 per cent of the theoretical amount of aniline expected from equation 26,

$$C_6H_5Cl + KNH_2 = C_6H_5NH_2 + KCl \tag{26}$$

$$C_6H_5NH_2 + KNH_2 = C_6H_5NHK + NH_3 \tag{27}$$

$$C_6H_5NHK + C_6H_5Cl = (C_6H_5)_2NH + KCl \tag{28}$$

together with smaller quantities of diphenylamine, which one might expect to result from reactions 27 and 28. Preliminary experiments have indicated that very little if any of the diphenylamine is formed in this way. This is in agreement with the work of Eatough (114) and White, Morrison, and Anderson (345). α-Bromonaphthalene, o- and p-chlorodiphenyl, o-chloroaniline, and o-dichlorobenzene likewise react readily with a liquid ammonia solution of potassium amide, but the reactions often appear complex. α-Fluoronaphthalene is more slowly converted by an excess of potassium amide in liquid ammonia at room temperatures to α-naphthylamine in fairly good yield. Fluorobenzene appears more inert and is not completely decomposed by potassium amide in the same time (34).

E. Triphenylgermanyl bromide, phenyl mercuric iodide, and tetraalkylammonium halides

Triphenylgermanium bromide, $(C_6H_5)_3GeBr$, is converted by potassium amide in liquid ammonia to triphenylgermanylamine, $(C_6H_5)_3GeNH_2$ (241). Under similar conditions, Chambers and Scherer (80) found that phenyl mercuric iodide, C_6H_5HgI, is converted to phenyl mercuric amine, $C_6H_5HgNH_2$.

Attempts of Franklin (123) to prepare tetramethylammonium amide, $(CH_3)_4N \cdot NH_2$, trimethylsulfonium amide, $(CH_3)_3S \cdot NH_2$, and diphenyliodonium amide, $(C_6H_5)_2I \cdot NH_2$, by the action of potassium amide on tetramethylammonium chloride, trimethylsulfonium iodide, and diphenyliodonium iodide, respectively, were unsuccessful. Kraus and his students are reëxamining the first of these reactions (236) and conclude that the tetraalkylammonium amides are unstable in ammonia.

VII. ALCOHOLS AND PHENOLS

In view of the fact that a substance as weakly acidic as triphenylmethane reacts with sodium amide and potassium amide in liquid ammonia (239), it may confidently be predicted that aliphatic alcohols and phenols will similarly be converted to alkali metal salts. Baumert and Landolt (25) and White, Morrison, and Anderson (345) report this to be the case in liquid ammonia

or benzene solution, although very few individual alcohols and phenols were examined. Sachs (300a), and White, Morrison, and Anderson (345), have observed that α- and β-naphthol react with sodium amide or potassium amide to form alkali metal salts. Sachs furthermore has examined the action of sodium amide upon β-naphthol at 200-220°C. in the presence of naphthalene, finding the chief product of the reaction to be 1-amino-6-naphthol. Hydrogen is evolved in approximately the amount corresponding to the equation

$$C_{10}H_7OH + 2NaNH_2 = C_{10}H_6(ONa)(NHNa) + H_2 + NH_3 \qquad (29)$$
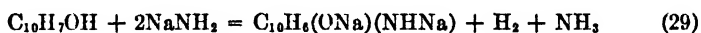
In two experiments, the total yield of mixed aminonaphthols was 35 and 56 per cent. Sachs also reports that α-naphthol, fused with sodium amide and naphthalene at 190°C., is converted in 20 per cent yield to 1-amino-5-naphthol. At higher temperatures, the formation of 1,5-naphthylenediamine predominates. Fused sodium amide converts phenol to benzene, but if this reaction is carried out in the presence of naphthalene, α-naphthylamine and 1,5-naphthylenediamine are formed, as has previously been reported.

Wooster (350) has found that potassium amide reacts with a liquid ammonia solution of benzohydrol, in the sense of equation 30, to form ammonia and dipotassium benzophenone.

$$(C_6H_5)_2CHOH + 2KNH_2 = 2NH_3 + (C_6H_5)_2C(K)(OK) \qquad (30)$$
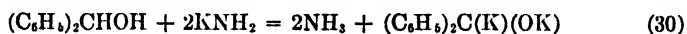
The latter substance may also be formed by the action of benzophenone upon an excess of a liquid ammonia solution of potassium (350).

Under similar conditions, benzopinacol is converted by potassium amide to ammonia and potassium benzophenone, a metal ketyl (349). The reaction follows the equation

$$\begin{array}{c}(C_6H_5)_2COH \\ | \\ (C_6H_5)_2COH\end{array} + 2KNH_3 = 2(C_6H_5)_2C(OK) + 2NH_3 \qquad (31)$$
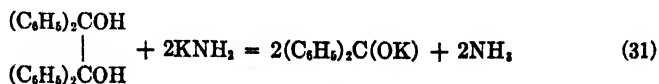
Benzopinacol   Potassium benzophenone

VIII. AMINES

A. Aliphatic amines

Titherley (330) states that sodium amide does not react with the aliphatic amines. The experimental conditions are not described. According to the experience of Wood and the senior author (38), the lower aliphatic amines do not react with potassium or sodium amide in liquid ammonia solution at ordinary temperatures.

Fernelius (119) has found that fused sodium amide reacts with the primary aliphatic amines with the formation of cyanamide (sodium ammonocarbonate) and a mixture of hydrogen and hydrocarbons. Fry (142, 144), Otto, Schulze, and Weitkamp have similarly found that alcohols may be changed to alkali carbonates, hydrocarbons, and hydrogen by fused bases of the water system.

B. Aromatic amines

Aromatic amines, on the other hand, are the ammonia analogues of the phenols of the water system. Consequently, they should be more prone to form alkali metal salts, and this in fact proved to be the case. It has long been known that aniline reacts with potassium and sodium amides, both in the presence and absence of liquid ammonia, to form a monosodium or monopotassium salt, in accordance with the following equation (344, 330, 259, 260).

$$C_6H_5NH_2 + NaNH_2 = NH_3 + C_6H_5NHNa \qquad (32)$$
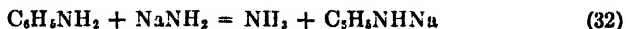
White, Morrison, and Anderson (344) are of the opinion that dipotassium anilide, $C_6H_5NK_2$, is not formed, except in small amounts, when aniline is treated with an excess of potassium amide in liquid ammonia at $-33°C.$, although White and Knight (343) state that disodium anilide, $C_6H_5NNa_2$, is stable in ammonia solution, if it is formed by reduction of azo- or nitro-benzene with sodium. Monosodium anilide can be alkylated in liquid ammonia by treatment with alkyl halides.

According to Meunier and Desparmet, Titherley, and White,

Morrison, and Anderson (259, 344, 331, 119), diphenylamine reacts with sodium or potassium amide in benzene or in ammonia to form a salt and this in turn is converted to N-ethyldiphenyl-amine by ethyl bromide (344), in the sense of the equation

$$(C_6H_5)_2NK + C_2H_5Br = KBr + (C_6H_5)_2NC_2H_5 \qquad (33)$$

Titherley (330) prepared the monosodium derivatives of aniline, p-toluidine, β-naphthylamine, and diphenylamine by the action of sodium amide upon a benzene solution of the amine.   Meunier and Desparmet (259, 260) similarly prepared sodium anilide and sodium diphenylamide.

Sachs (300a) found that α-naphthylamine, fused with a mixture of sodium amide and naphthalene at 230°C., was converted in 47 per cent yield to a fairly pure 1,5-naphthylenediamine with evo-lution of hydrogen.   β-Naphthylamine, under similar conditions, was converted to 2,5-naphthylenediamine in about 45 per cent yield, together with a small amount of an *ortho* diamine, probably 2,3-naphthylenediamine.   Hydrogen was evolved, but not in quite the expected quantity, pointing to the possible formation of hydronaphthalenes.   The main reaction follows the equation

$$C_{10}H_7NH_2 + NaNH_2 = H_2 + C_{10}H_6(NH_2)_2 \text{ (as a sodium salt)} \qquad (34)$$

Kraus and Wooster (241), report that triphenylgermanylamine, $(C_6H_5)_3GeNH_2$, reacts with potassium amide in liquid ammonia to form a salt of the composition, $(C_6H_5)_3GeNHK$.

IX. ALDEHYDES AND ALDEHYDE AMMONIAS

A. Aliphatic aldehydes, trimeric ethylidenimine

Aside from an earlier observation of Meunier and Desparmet (259, 260) to the effect that sodium amide reacts with acetalde-hyde, possibly to form $CH_3CH{=}NNa$, the literature fails to record that anyone has directly treated aldehydes with metallic amides.   Strain (325) has obtained trimolecular ethylidenimine, a close although not exact ammonia analogue of paraldehyde, by treating a liquid ammonia solution of aldehyde ammonia with the almost insoluble calcium amide.   It may be recalled in this con-

nection that Delépine (109) regards aldehyde ammonia as having the formula, $(CH_3CH=NH)_3 \cdot 3H_2O$, which represents a trihydrate of a trimolecular ethylidenimine. Removal of water from this compound in a vacuum desiccator gives the anhydrous trimer, of the probable constitution,

$$
\begin{array}{c}
NH \\
CH_3—CH \quad CHCH_3 \\
| \quad\quad | \\
NH \quad NH \\
CH \\
| \\
CH_3
\end{array}
$$
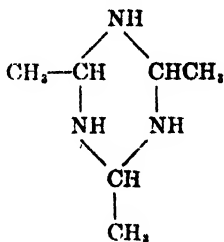
This is the compound that Strain has prepared in liquid ammonia. Potassium amide, presumably because of its high solubility in this solvent, converts acetaldehyde ammonia into dark colored condensation products, in much the fashion that potassium hydroxide causes the formation of colored aldehyde resins from acetaldehyde.

B. Aromatic aldehydes

Haller and Bauer (170a) treated benzaldehyde with sodium amide in benzene or toluene and obtained benzamide (undoubtedly as the sodium salt) and benzyl alcohol, in accordance with the equation

$$2C_6H_5CHO + NaNH_2 = C_6H_5CH_2OH + C_6H_5CONHNa \qquad (35)$$

It is probable that the benzyl alcohol is converted by an excess of sodium amide to sodium benzylate. Both benzyl alcohol and benzamide are obtained when this mixture is hydrolyzed. Since benzamide is a mixed aquoammonobenzoic acid (128), this is clearly an example of the Cannizzaro reaction. Anisic aldehyde is similarly converted to anisamide and anisyl alcohol. Kasiwagi (229) has verified the work of Haller and Bauer on the reaction between benzaldehyde and sodium amide, and has in addition found that furfuraldehyde is converted to furyl alcohol and pyromucic acid (or its amide?) by sodium amide in boiling toluene.

X. ALDIMINES, HYDRAMIDES, AND SCHIFF BASES

A. Benzylideneimine and hydrobenzamide

It has long been known that benzaldehyde reacts with aqueous ammonia to form hydrobenzamide, possibly in the manner of the following scheme.

$$3C_6H_5CHO \xrightarrow{+3NH_3} (3C_6H_5CH{=}NH) \xrightarrow{-NH_3} (C_6H_5CH{=}N)_2{=}CHC_6H_5 \quad (36)$$
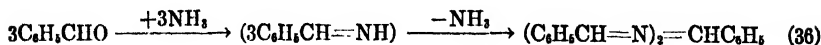
Benzaldehyde   Benzylideneimine   Hydrobenzamide

The first reaction, in which benzaldehyde is converted to the assumed intermediate, benzylideneimine, may be regarded as an ammonolysis of an aquo aldehyde to an aldehyde-alcohol of the ammonia system (321). The unfamiliar complexity of a substance that is simultaneously an alcohol and an aldehyde because of a single grouping within the molecule, is to be attributed to the trivalence of nitrogen as compared with the divalence of oxygen.
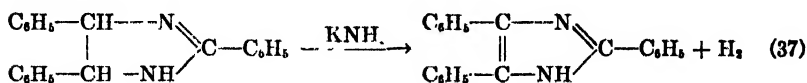
When three molecules of benzylideneimine lose ammonia to form hydrobenzamide, a compound is produced in which no hydrogen atoms are attached to nitrogen, yet this substance is not a strict ammonia analogue of benzaldehyde, because of the fact that the $C_6H_5CH{=}$ group on the right side of the formula is attached by single bonds to each of two nitrogens. Therefore, hydrobenzamide is not only an aldehyde, but also an acetal of the ammonia system.

With these brief definitions of ammono aldehyde-alcohols and ammono aldehyde-acetals in mind, it is possible to understand the often apparently complex effects of potassium amide upon substances of this class.

Strain (321) found that benzylideneimine could be prepared by the long continued action of liquid ammonia at room temperatures upon hydrobenzamide, a direct reversal of the second step of equation 36. With potassium and sodium amides in liquid ammonia, benzylidineimine forms very soluble, deep red colored salts of the typical composition, $C_6H_5CH{=}N \cdot K$. When heated with an excess of a liquid ammonia solution of potassium amide for one day at 210°C., the potassium salt is converted to potassium

benzamidine, $C_6H_5 \cdot C(NH)NHK$ (a potassium ammonobenzoate), benzylamine, $C_6H_5CH_2NH_2$ (an ammonobenzyl alcohol), and lophine, a product of the action of potassium amide upon amarine. Amarine is known to be formed by the slow decomposition of benzylidencimine in liquid ammonia (323).
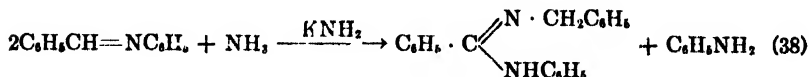
Amarine, which is formed from hydrobenzamide by a process akin to a benzoin condensation (320), is converted by potassium amide in liquid ammonia to lophine and hydrogen, in accordance with the equation

$$C_6H_5—CH---N \backslash \quad \xrightarrow{KNH_2} \quad C_6H_5—C---N$$

$$\begin{array}{ccc} C_6H_5—CH----N \\ | \qquad\qquad \big\rangle C—C_6H_5 \\ C_6H_5—CH\ —NH \end{array} \xrightarrow{KNH_2} \begin{array}{ccc} C_6H_5—C----N \\ \| \qquad\qquad \big\rangle C—C_6H_5 + H_2 \quad (37) \\ C_6H_5—C—NH \end{array}$$

A reaction of this type is especially noteworthy because it takes place in liquid ammonia at room temperatures. Potassium hydroxide attacks many organic compounds with the evolution of hydrogen, but these reactions as a rule occur only at elevated temperatures (142, 143, 144).

B. Schiff bases

Schiff bases, $R \cdot CH{=}N \cdot R'$, are ammono aldehyde-acetals. In conformity with this view, Strain (323a) found that benzylidene-aniline, $C_6H_5CH{=}NC_6H_5$, is converted into benzylphenylbenz-amidine by the action of a solution of two or more equivalents of potassium amide in liquid ammonia at room temperatures, in accordance with the equation

$$2C_6H_5CH{=}NC_6H_5 + NH_3 \xrightarrow{KNH_2} C_6H_5 \cdot C \begin{array}{c} \diagup N \cdot CH_2C_6H_5 \\ \diagdown NHC_6H_5 \end{array} + C_6H_5NH_2 \quad (38)$$

Benzylphenylbenzamidine

Benzylphenylbenzamidine is at the same time a benzyl and a phenyl ester of ammonobenzoic acid (benzamidine, $C_6H_5 \cdot C(={}$ $NH)NH_2$). The overall reaction is therefore analogous to the formation of benzyl benzoate from potassium hydroxide and benzaldehyde. The phenyl group attached to the third valence of the nitrogen of benzylideneaniline naturally complicates matters somewhat, in that the reaction product still contains one

phenyl group, while another one has been eliminated as aniline. It should be noted that Lachmann (242) has obtained evidence for the intermediate formation of benzyl benzoate in the Cannizzaro reaction between sodium hydroxide and benzaldehyde (cf. 143).

Pyridine, quinoline, isoquinoline, and their derivatives, which may be regarded as cyclic Schiff bases (76, 35), will be discussed further on in this article.
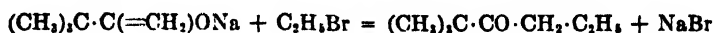
XI. KETONES

A. Aliphatic ketones

Titherley (334) treated a solution of dry acetone in benzene with sodium amide and found that a gelatinous precipitate was formed, with the simultaneous evolution of ammonia. The precipitate, consisting of the sodium salts of the enolic forms of the various condensation products, was hydrolyzed and the benzene layer fractionated to give mesityl oxide, phorone, and isophorone. Freund and Speyer (138) repeated the work of Titherley without using benzene as a medium, and report isophorone to be the chief product.

Strain (324) prepared the sodium salt of the enol form of acetone by treating acetone with sodium amide in liquid ammonia. (For the preparation of this salt in ether, etc., see reference 27a.)

$$(CH_3)_2CO + NaNH_2 = CH_3C(=CH_2)ONa + NH_3 \qquad (39)$$
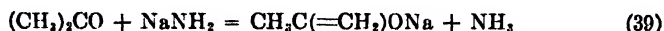
Pinacolone, $(CH_3)_3C \cdot CO \cdot CH_3$, refluxed for one to three hours with sodium amide under ether, is converted to the sodium salt of the enolic modification, and this readily reacts with the lower saturated and unsaturated aliphatic halides to form monoalkyl pinacolones. Di- and tri-alkyl derivatives of the general formulas, $(CH_3)_3C \cdot CO \cdot CHRR'$ and $(CH_3)_3C \cdot CO \cdot CRR'R''$ are successively obtained by repetitions of the alkylation process. The formation of a monoalkyl pinacolone may be represented as follows (200, 177a).

$$(CH_3)_3C \cdot CO \cdot CH_3 + NaNH_2 = (CH_3)_3C \cdot C(=CH_2)ONa + NH_3 \qquad (40)$$

$$(CH_3)_3C \cdot C(=CH_2)ONa + C_2H_5Br = (CH_3)_3C \cdot CO \cdot CH_2 \cdot C_2H_5 + NaBr$$

According to Haller (193, 194, 178, 177a), aliphatic and mixed aliphatic-aromatic ketones containing the residues CH_2= and CHR= attached to a carbonyl group are capable of reaction with sodium amide, the resulting salts reacting with the lower alkyl halides to form homologous ketones. Acetone is an exception, in that phorone and other condensation products are formed, and it may be inferred that some of the other less complex aliphatic ketones will behave in the same manner. Pentanone-3, methyl isohexyl ketone and others of similar complexity have been successfully alkylated (353).

B. Mixed aliphatic-aromatic ketones

1. The alkylation of mixed ketones of the type of acetophenone and acetonaphthone. Claisen and Feyerabend (96), following the earlier work of Haller (166) on the alkylation of menthone with the use of sodium amide and an alkyl halide, found that acetophenone, dissolved in benzene, readily reacts with sodium amide to form a soluble sodium salt, together with ammonia. Haller and Bauer (172b) later demonstrated that the reaction follows the equation

$$C_6H_5 \cdot CO \cdot CH_3 + NaNH_2 = NH_3 + C_6H_5C(ONa) = CH_2 \text{ (or, } C_6H_5 \cdot CO \cdot CH_2Na) \text{ (41)}$$
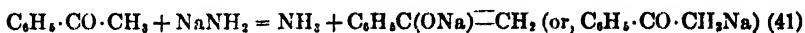
The first formula, representing the product as a derivative of the enol form of acetophenone, is undoubtedly to be preferred. Hydrolysis of this salt by water alone results in the almost quantitative regeneration of the acetophenone. This is not the case if the sodium salt is heated for some time in xylene, since a small quantity of dypnone, $C_6H_5(CH_3)C=CH \cdot CO \cdot C_6H_5$, is formed, together with a larger amount of a resinous condensation product from which no definite compounds can be isolated. The presence of sodium hydroxide in the sodium amide increases the relative amount of dypnone in the above reaction (177).

Strain (324) has obtained sodium acetophenone in definite crystalline form by carrying out the reaction of equation 41 in liquid ammonia. The senior author has prepared potassium acetophenone by the action of acetophenone on potassium quinaldine in liquid ammonia (30).

Claisen and Feyerabend (96) slowly added sodium amide to equivalent proportions of a solution of acetophenone and ethyl iodide in anhydrous ether, obtaining a reaction mixture which yielded ethyl acetophenone (i.e., n-butyrophenone) on hydrolysis, together with smaller amounts of diethylacetophenone and unchanged acetophenone. The two reactions may be expressed by the following equations.

$$C_6H_5 \cdot C(ONa) = CH_2 + C_2H_5I = C_6H_5 \cdot CO \cdot CH_2CH_2CH_3 + NaI \qquad (42)$$

The butyrophenone is converted either by the sodium amide or by the sodium acetophenone to a sodium salt, and this may be ethylated in accordance with the equation

$$C_6H_5 \cdot C(ONa) = CHCH_2CH_3 + C_2H_5I = C_6H_5 \cdot CO \cdot CH(C_2H_5)_2 + NaI \qquad (43)$$
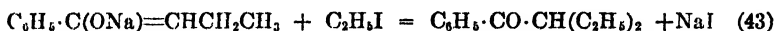
The reaction between ethylacetophenone and sodium acetophenone to give acetophenone and sodium ethylacetophenone is undoubtedly reversible.

Claisen and Feyerabend in a similar manner have obtained benzylacetophenone from sodium amide, acetophenone, and benzyl chloride. In a repetition of this reaction, Haller and Bauer (175) have isolated in addition a small quantity of dibenzylacetophenone.
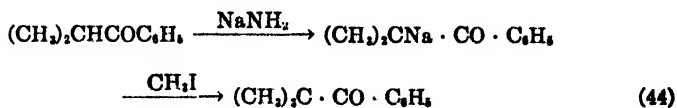
A number of years later, Haller and Bauer (190, 200, 198a, 172) began a rather extended series of investigations on the alkylation of acetophenone and its derivatives, with the result that they were able to prepare a large number of ketones of the general formulas, $C_6H_5 \cdot CO \cdot CH_2R$, $C_6H_5 \cdot CO \cdot CHRR'$, and $C_6H_5 \cdot CO \cdot CRR'R''$, where R, R' and R'' are usually methyl, ethyl, propyl, allyl, or benzyl. The aromatic groups, such as phenyl, as well as the higher aliphatic groups, can not be introduced into acetophenone by this method.

The manner in which a mixed aliphatic-aromatic ketone is alkylated will be made clear by the description of a typical experiment. Sodium amide, ground to a powder under ether or some other inert liquid, is introduced into a balloon flask provided with a dropping funnel and a reflux condenser terminated by a mercury bubbler. A suitable amount of ether or benzene is then added,

and the ketone which is to be alkylated is introduced gradually through the dropping funnel. The reaction, whose velocity depends upon the nature of the ketone, is complete when the evolution of ammonia (equation 41) has ceased, this generally occurring in from thirty minutes to three hours. The sodium derivative of the ketone is often soluble in the ether or benzene used as a reaction medium. Maintaining the solvent at the boiling temperature, an alkyl halide is slowly introduced through the dropping funnel. The reaction is often vigorous, and with methyl and ethyl iodides is terminated in a short while. With less reactive halides, prolonged heating of the reaction mixture is often necessary. The substitution having taken place, water is cautiously added to dissolve the sodium halide, the ether or benzene layer is washed several times with water and finally distilled. The residue remaining after the evaporation of the solvent is fractionated in a vacuum to give the desired alkylated ketones.

Haller and Bauer, Dumesnil, Albesco, Blondeau, Ramart-Lucas (190, 192, 200, 198a, 283, 172, 110, 3, 43, 204) and others who have used this method for the alkylation of the mixed alkyl aryl ketones have concerned themselves principally with the preparation of the di- and tri-substituted acetophenones of the general formulas, $C_6H_5 \cdot CO \cdot CHRR'$ and $C_6H_5 \cdot CO \cdot CRR'R''$. It will be impossible to give more than a very few specific examples.

(1) Trimethylacetophenone, $(CH_3)_3C \cdot CO \cdot C_6H_5$, or pivalophenone, was prepared by Nef (273) in poor yield by heating a mixture of acetophenone, methyl iodide, and aqueous sodium hydroxide in a sealed tube. It was very difficult to effect a satisfactory separation of this compound from the mono- and dimethylacetophenones which were formed at the same time. Haller and Bauer (172a) discarded the synthesis of trimethylacetophenone by the successive methylation of acetophenone with sodium amide and methyl iodide in favor of the simpler preparation from phenyl isopropyl ketone, in accordance with the equation

$$(CH_3)_2CHCOC_6H_5 \xrightarrow{\quad NaNH_2 \quad} (CH_3)_2CNa \cdot CO \cdot C_6H_5$$

$$\xrightarrow{\quad CH_3I \quad} (CH_3)_3C \cdot CO \cdot C_6H_5 \qquad\qquad (44)$$

The yields generally ranged between 88 and 93 per cent of the theoretical, indicating conclusively the marked superiority of sodium amide over sodium hydroxide in this synthesis.
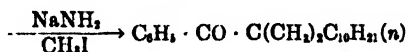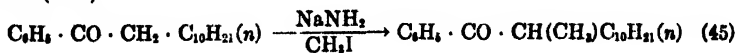
(2) Ethyl phenyl ketone, $C_2H_5 \cdot CO \cdot C_6H_5$, is converted by sodium amide in benzene to a sodium salt, $CH_3CH=C(ONa) \cdot C_6H_5$, which reacts readily with ethyl iodide to form methylethylacetophenone, $(CH_3)(C_2H_5)CH \cdot CO \cdot C_6H_5$, together with smaller quantities of methyldiethylacetophenone, $(CH_3)(C_2H_5)_2 \cdot CO \cdot C_6H_5$. The two were separated by fractional distillation in a vacuum. The former, by the successive action of sodium amide and n-propyl iodide, was changed to methylethyl-n-propylacetophenone, $(CH_3)(C_2H_5)(n\text{-}C_3H_7)COC_6H_5$ (173). Here, as elsewhere, alkylation has occurred exclusively on the α-carbon atom.

(3) Phenylethylpropiophenone, $(C_6H_5)(C_2H_5)CHCH_2 \cdot CO \cdot C_6H_5$, reacts with sodium amide in benzene to form a sodium salt, $(C_6H_5)(C_2H_5)CHCHNa \cdot COC_6H_5$, and this in turn reacts with methyl iodide to give phenylmethylethylpropiophenone, $(C_6H_5)(C_2H_5)CH \cdot CH(CH_3) \cdot CO \cdot C_6H_5$ (4).

Previously, a reference has been made to the impossibility of introducing the higher alkyl groups into acetophenone and related ketones by an extension of the methods which have just been described. This statement is amply supported by the work of Haller and his associates. n-Propylacetophenone (n-valerophenone) is obtained in poor yield, unaccompanied by higher alkylated ketones (176), by treating acetophenone with sodium amide and then with n-propyl iodide. At the same time, a small quantity of dypnone, $C_6H_5C(CH_3)=CH \cdot CO \cdot C_6H_5$, is formed by the condensation of two molecules of acetophenone with the elimination of a molecule of water. (Compare the formation of mesityl oxide from acetone.) Isobutyl iodide and sodium amide convert acetophenone into dypnone and other condensation products, without the formation of appreciable quantities of alkylated ketones (177).

The higher branched chain homologues of acetophenone must therefore be prepared by starting with ketones of the general formula, $C_6H_5 \cdot CO \cdot CH_2C_nH_{2n+1}$ or $C_6H_5 \cdot CO \cdot CHRR'$, which may be converted to sodium salts by the action of sodium amide and then to the desired alkylated acetophenones by means of the

lower alkyl halides.   In this manner, α-methyl and α, α-dimethyllaurophenone may be prepared in fair yield from laurophenone (174).

$$C_6H_5 \cdot CO \cdot CH_2 \cdot C_{10}H_{21}(n) \xrightarrow[CH_3I]{NaNH_2} C_6H_5 \cdot CO \cdot CH(CH_3)C_{10}H_{21}(n) \quad (45)$$

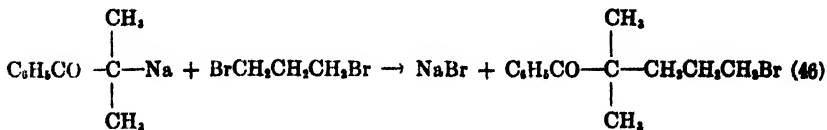$$\xrightarrow[CH_3I]{NaNH_2} C_6H_5 \cdot CO \cdot C(CH_3)_2C_{10}H_{21}(n)$$

α- and β-Acetonaphthones may be alkylated in the same manner as acetophenone, again with the limitation that only the lower alkyl groups may be introduced (340).
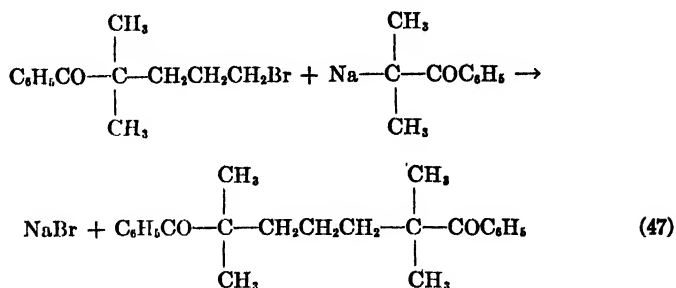
The allyl group, for some unknown reason, cannot be directly introduced into acetophenone or into the acetonaphthones, as can the methyl or ethyl groups (173, 190, 200, 204).   The allyl alkyl and allyl dialkyl ketones can be prepared only by the alkylation of previously formed ω-monoallylacetophenones or acetonaphthones.   It is interesting to note that monoallylacetophenone, reacting successively with sodium amide and allyl iodide, is converted into di- and tri-allylacetophenone.

A tabulation of the numerous compounds prepared by Haller and members of the contemporary French school appears inadvisable in this article, not only because of the limitations of space, but particularly because of the existence of an excellent review of this field by Haller himself (161).   Therefore, the abbreviation of this work, and the simultaneous inclusion in other parts of this article of numerous reactions of less interest to the synthetic organic chemist is for the sole purpose of describing the effect of the alkali amides on a maximum number of compound types.

`2. The action of ethylene and trimethylene dihalides on the sodium salts of mixed aliphatic-aromatic ketones.   Ethylene dibromide and ethylene chlorobromide are indifferent toward the sodium salt of isopropyl phenyl ketone, whatever the solvent.   Trimethylene dibromide and chlorobromide, on the other hand, react with sodium isopropyl phenyl ketone, first to form a monobrominated ketone (196, 218),
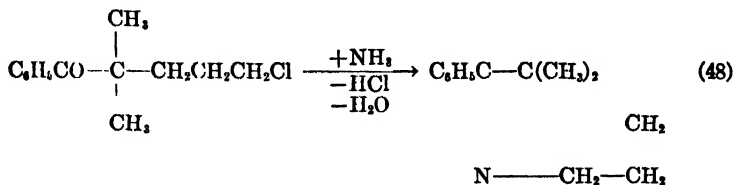
$$C_6H_5CO-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-Na + BrCH_2CH_2CH_2Br \rightarrow NaBr + C_6H_5CO-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2CH_2CH_2Br \quad (46)$$

which is difficult to isolate in a pure state, and then, with a second molecule of the sodium salt, a diketone.

$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\text{CO—C—CH}_2\text{CH}_2\text{CH}_2\text{Br} \\
| \\
\text{CH}_3
\end{array}
+
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{Na—C—COC}_6\text{H}_5 \\
| \\
\text{CH}_3
\end{array}
\rightarrow
$$

$$
\text{NaBr} +
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\text{CO—C—CH}_2\text{CH}_2\text{CH}_2 \\
| \\
\text{CH}_3
\end{array}
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{—C—COC}_6\text{H}_5 \\
| \\
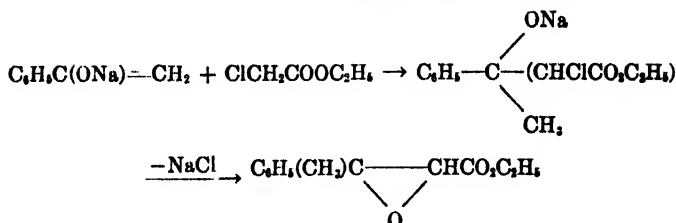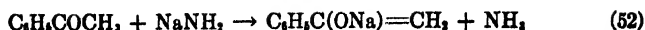\text{CH}_3
\end{array}
\tag{47}
$$

The representation of the sodium salt above as a derivative of the keto form is only for purposes of convenience.

This synthesis has been extended by Haller and Ramart (218), Dumesnil (113), and Billon (39) the last named author having succeeded in preparing in a pure state chlorinated ketones of the type, $(\text{CH}_3)_2\text{CH} \cdot \text{CO} \cdot \text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$, which are aliphatic analogues of the ketones of equation 46.

The intermediate halogenated ketone of equation 46 may be converted to a tetrahydropyridine derivative by heating with alcoholic ammonia in a sealed tube (217). In this way, 2-phenyl-3,3-dimethyltetrahydropyridine may be made from 2-methyl-2-benzoyl-5-chloropentane.
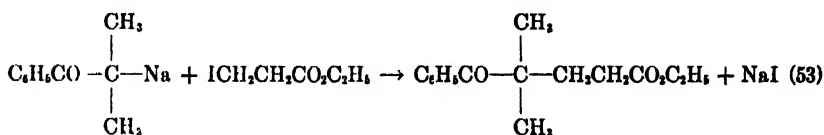
$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\text{CO—C—CH}_2\text{CH}_2\text{CH}_2\text{Cl} \\
| \\
\text{CH}_3
\end{array}
\xrightarrow[\substack{-\text{HCl} \\ -\text{H}_2\text{O}}]{+\text{NH}_3}
\text{C}_6\text{H}_5\text{C—C}(\text{CH}_3)_2
\tag{48}
$$

$$
\begin{array}{cc}
 & \text{CH}_2 \\
\text{N} & \text{—CH}_2\text{—CH}_2
\end{array}
$$

3. The action of epihalohydrins on the sodium salts of dialkyl acetophenones. Sodium acetophenone reacts with the epihalo-hydrins to give viscous products of an indefinite nature (219). On the other hand, the sodium derivative of the more complex phenyl isopropyl ketone reacts with epichlorohydrin and epi-bromohydrin to give the oxide of propylenedimethylacetophenone, in accordance with the equation
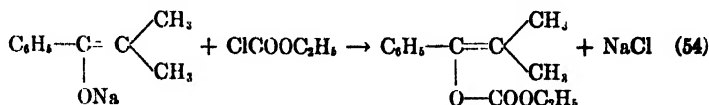
$$\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C_6H_5CO—C—Na}} + BrCH_2CH—CH_2 = NaBr + \underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C_6H_5CO—C—CH_2CHCH_2}} \quad (49)$$

4. The action of monochloroacetic esters on ketones in the presence of sodium amide. Claisen and Feyerabend (97) slowly added sodium amide to a solution of equimolecular amounts of acetophenone and ethyl monochloroacetate in ether, anticipating thereby the preparation of a 1.,4-diketone. Unexpectedly, a good yield of β-phenylmethylglycidic ester was obtained, in a manner which may be represented as follows: (1) Addition of sodium amide to the carbonyl group of the ketone,

$$C_6H_5 \cdot CO \cdot CH_3 + NaNH_2 = C_6H_5C(ONa)(NH_2)CH_3 \quad (50)$$

(2) Condensation of this addition product with chloroacetic ester, with elimination of ammonia, to form

$$C_6H_5(CH_3)C(ONa) \cdot CHCl \cdot COOC_2H_5$$

(3) Elimination of sodium chloride with the formation of the glycidic ester.

$$\underset{CH_3}{\overset{C_6H_5}{>}}C\text{------}CHCOOC_2H_5$$

The free glycidic acid, which results when the ester is saponified, readily passes into an aldehyde by loss of carbon dioxide, in the sense of the equation

$$\underset{R'}{\overset{R}{>}}C\text{------}CH—COOH \rightarrow \underset{R'}{\overset{R}{>}}CH—CHO + CO_2 \quad (51)$$

Accordingly, this affords a method for the preparation from a ketone of an aldehyde containing one more carbon atom.

Quite recently, Rutovskii and Daev (292) have reinvestigated this reaction and favor a mechanism involving the sodium salt of the enol form of acetophenone.

$$C_6H_5COCH_3 + NaNH_2 \rightarrow C_6H_5C(ONa)=CH_2 + NH_3 \qquad (52)$$

$$C_6H_5C(ONa)=CH_2 + ClCH_2COOC_2H_5 \rightarrow C_6H_5\underset{\underset{CH_3}{|}}{\overset{\overset{ONa}{/}}{C}}(CHClCO_2C_2H_5)$$

$$\xrightarrow{-NaCl} C_6H_5(CH_2)C\underset{\underset{O}{\diagdown\diagup}}{\underset{}{\qquad}}CHCO_2C_2H_5$$

Strangely enough, the elimination of chlorine does not occur in either of the above mechanisms until the last step of the reaction.

5. *The action of α-iodoacetic and β-iodopropionic esters on the sodium salts of ketones.* These reactions proceed in the expected manner, that is, in accord with the type equation

$$C_6H_5CO-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-Na + ICH_2CH_2CO_2C_2H_5 \rightarrow C_6H_5CO-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2CH_2CO_2C_2H_5 + NaI \quad (53)$$

to form γ- or δ-ketonic esters (219a).

6. *The action of chlorocarbonic esters on the sodium salts of ketones.* Haller and Bauer found (195) that sodium isopropyl phenyl ketone reacts with ethyl chlorocarbonate in benzene to give a derivative of the enol form of the ketone,

$$C_6H_5-\underset{\underset{ONa}{|}}{C}=C\overset{\diagup CH_3}{\diagdown CH_3} + ClCOOC_2H_5 \rightarrow C_6H_5-\underset{\underset{O-COOC_2H_5}{|}}{C}=C\overset{\diagup CH_3}{\diagdown CH_3} + NaCl \quad (54)$$

It will be recalled that chlorocarbonic ester similarly reacts with sodium acetoacetic ester to give a substitution product of the enol, of the constitution (264, 94)

$$CH_3C=CH-COOC_2H_5$$
$$\underset{O-COOC_2H_5}{|}$$
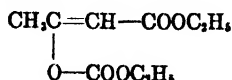
Sodium pentamethylacetone, $(CH_3)_3CC(ONa)=C(CH_3)_2$, is similarly converted by ethyl chlorocarbonate to the enolic ester (186a),

$$(CH_3)_2C-C \overset{OCO_2C_2H_5}{\underset{\displaystyle C}{\diagup}} \quad CH_3$$

(CH$_3$)$_2$C—C with OCO$_2$C$_2$H$_5$ and CH$_3$, double bond to C, bearing CH$_3$
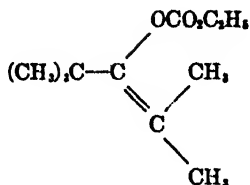
while sodium acetophenone gives a mixture of products of the formulas,

$$C_6H_5COCH\diagdown \begin{array}{c} COOC_2H_5 \\ COOC_2H_5 \end{array} \quad \text{and} \quad \begin{array}{c} C_6H_5C\!\!=\!\!CHCOOC_2H_5 \\ | \\ O\!-\!COOC_2H_5 \end{array}$$
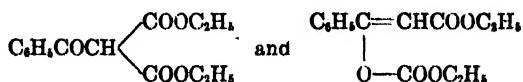
The first is obtained by the di-C alkylation of acetophenone, the second probably by successive C and O alkylations (195, 186).

7. *The action of acid chlorides on the sodium salts of ketones.* As an illustration, benzoyl chloride reacts with the sodium salts of a number of ketones to give a β-diketone, together with the corresponding enolic isomer (197, 21).

$$C_6H_5CO-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-Na + C_6H_5COCl \rightarrow C_6H_5CO-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-COC_6H_5 + NaCl \quad (55)$$

$$\text{and} \quad C_6H_5C\diagdown \begin{array}{c} OCOC_6H_5 \\ C(CH_3)_2 \end{array}$$
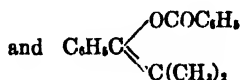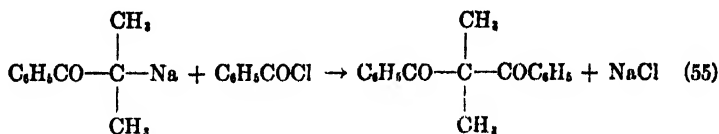
C. Cyclic ketones

1. *The alkylation of substituted cyclopentanones, thujone, isothujone, and indanone.* Cyclopentanone undergoes a crotonaldehyde type condensation in the presence of sodium amide to form cyclopentylidenecyclopentanone, in accordance with the equation

$$\begin{array}{c} CH_2\!-\!CH_2 \\ | \qquad | \\ CH_2 \quad CH_2 \\ \diagdown \quad \diagup \\ CO \end{array} + \begin{array}{c} CH_2\!-\!CH_2 \\ | \qquad | \\ CH_2 \quad CH_2 \\ \diagdown \quad \diagup \\ CO \end{array} \xrightarrow{\text{NaNH}_2} \begin{array}{c} CH_2\!-\!CH_2 \\ | \qquad | \\ CH_2 \quad CH_2 \quad CH_2\!-\!CH_2 \\ \diagdown \quad \diagup \qquad \qquad | \\ C\!=\!\!=\!\!C \quad CH_2 \\ \diagdown \quad \diagup \\ CO \end{array} + H_2O \quad (56)$$
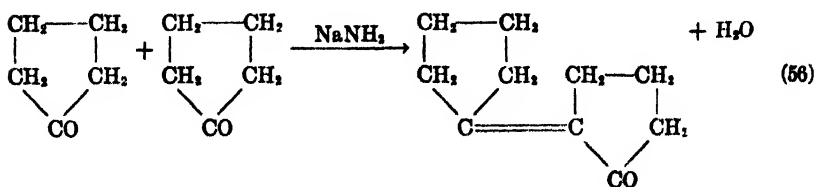
If suitable precautions are observed, one may prepare α-methyl-cyclopentanone in poor yield by the successive action of sodium amide and methyl iodide on the unsubstituted ketone (211; cf. 27a).

β-Methylcyclopentanone, like cyclopentanone itself, undergoes the crotonaldehyde type condensation of equation 56, and it is not possible to prepare alkylation products in satisfactory yield (211). α-Methyl- and α,β'-dimethyl-cyclopentanone, may, on the other hand, be alkylated in the usual manner. As an end-product of a series of successive alkylations, an α,α,α',α'-tetra-substituted or an α,α,α',α',β'-pentasubstituted cyclopentanone is obtained. (See also reference 358.)

It was found difficult even to introduce the n-propyl group into cyclopentanone or its derivatives, while the introduction of the higher alkyl groups was in general impossible. It will be recalled that similar difficulties were encountered in the alkylation of acetophenone.

Thujone   Isothujone
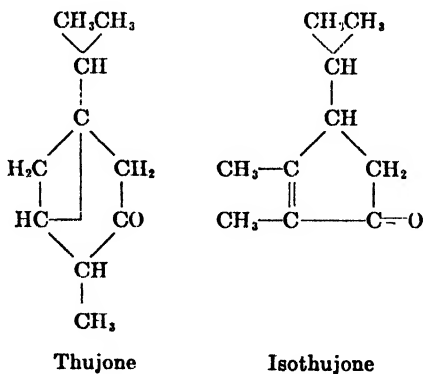
Both thujone and isothujone contain cyclopentanone rings and are capable of alkylation in the same manner as the simple deriva-tives of cyclopentanone. Three alkyl groups may be introduced in place of the three available α and α' hydrogen atoms of thujone, while isothujone can be alkylated only two times (168, 169a).

Monomethyl-, ethyl-, propyl- and allyl-thujones were pre-pared in this manner, and from the first and last named, dimethyl-, diallyl-, and triallyl-thujones were obtained by further alkylation. The inability to synthesize a trimethylthujone is of interest.

Indanone,

$$C_6H_4 \underset{CO}{\overset{CH_2}{<}} CH_2$$
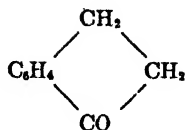
has two hydrogen atoms in the α position with respect to carbonyl, and these may be replaced successively by methyl groups in the usual manner (185).

2. The alkylation of camphor. Camphor,

$$C_8H_{14} \underset{C=O}{\overset{CH_2}{<}}$$
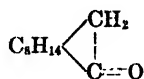
is readily converted by sodium amide in ether or benzene to a sodium salt,

$$C_8H_{14} \underset{C-ONa}{\overset{CH}{<}}$$
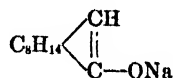
which reacts with the lower aliphatic halides to form monoalkyl camphors. A second alkyl group may be introduced by a repetition of this process (164, 181, 213, 214).

p-Aminobenzylidenecamphor and other compounds of a like nature may readily be formed by the action of *p*-aminobenzaldehyde or a homologue upon the sodium salt of camphor in an inert liquid (191, 208, 164).

$$C_8H_{14} \overset{CH}{\underset{C-ONa}{<}} + NH_2-C_6H_4-CHO(p) = NaOH +$$

$$C_8H_{14} \overset{C=CHC_6H_4-NH_2(p)}{\underset{C=O}{<}} \qquad (57)$$
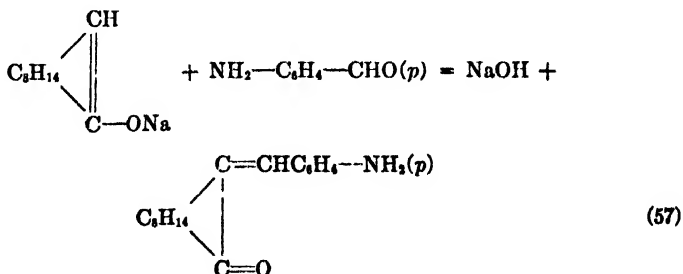
Substituted benzylidene camphors do not appear to have been made by the action of aromatic aldehydes upon free camphor. It will be recalled that benzaldehyde condenses with many ketones

containing an active methylene group, although often rather slowly and in the presence of zinc chloride or a similar dehydrating agent.

Camphorcarboxylic acid,

$$C_8H_{14} \diagdown \begin{array}{l} CH-COOH \\ | \\ C=O \end{array}$$

(as sodium salt)
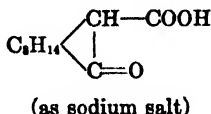
is obtained by passing dry carbon dioxide through sodium camphor under benzene (75).

Bromocamphor reacts slowly and incompletely with sodium amide in boiling benzene. Aminocamphor is formed only in traces, while the chief isolable product appears to be sodium camphor, which was identified by conversion to camphorcarboxylic acid. The yield of the latter, calculated on the basis of the bromocamphor, is 30 per cent (75).

3. The alkylation of cyclohexanone, menthone, and their derivatives. According to Haller (169), sodium amide converts cyclohexanone in a large measure to cyclohexylidenecyclohexanone by a crotonaldehyde type condensation similar to that of equation 56 (cf. reference 27a). It is therefore not possible to alkylate cyclohexanone itself with altogether satisfactory results, although Haller has reported the preparation of a number of alkylated derivatives. Cornubert (104, 105) in a subsequent investigation finds that the extent to which this condensation takes place is a maximum at about room temperatures, but is a minimum in the more dilute ethereal solutions. Bearing this in mind, he succeeded in synthesizing a series of allyl- and methylallyl-cyclohexanones. All four hydrogen atoms in the α and α' positions with respect to carbonyl may be replaced by allyl groups.

Gardner, Perkin, and Watson (148a) and Luff and Perkin (148a) prepared cyclohexanone-2-carboxylic acid,

$$\begin{array}{ccc} & CH_2CH-COOH & \\ \diagup & & \diagdown \\ CH_2 & & CO \\ \diagdown & & \diagup \\ & CH_2CH_2 & \end{array}$$

(as sodium salt)
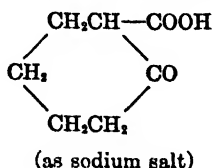
by treating cyclohexanone successively with sodium amide and carbon dioxide in ether. α-, β-, and γ-Methylcyclohexanones may be converted to carboxylic acids in a similar manner.

The condensation of equation 56 is evident to some extent even with α-, β-, and γ-methylcyclohexanones. Nevertheless, it is possible to alkylate all three of these compounds in a satisfactory manner (170, 166, 167, 216, 209, 212, 359).

When α-methylcyclohexanone is monoalkylated and γ-methylcyclohexanone is dialkylated, both alkyl groups are found to be attached to the same carbon atom, as may be shown by the fact that the products contain a —CH_2CO— group which condenses with benzaldehyde (170, 9, 212a, 360). Subsequent investigations revealed the fact that there are formed smaller quantities of the isomeric products in which the two entering alkyl groups are attached to different (α and α') carbon atoms (360). All available α and α' hydrogen atoms of these two substances may be replaced by allyl groups.

β-Methylcyclohexanone, on the other hand, is first alkylated in the α' position, isopropyl iodide thus reacting with the sodium derivative of the ketone to form isopropylmethylcyclohexanone, or menthone (216).

$$
\begin{array}{c}
CH_3 \\
H_2C \quad\diagup\diagdown\quad CHCH_3 \; (\beta) \\
| \qquad\qquad | \\
(\alpha')H_2C \qquad CH_2 \;\; (\alpha) \\
\diagdown\quad\diagup \\
CO
\end{array}
\quad \xrightarrow{\;NaNH_2\;} \quad Na \; salt
$$

$$
\xrightarrow{\;(CH_3)_2CHI\;} \quad
\begin{array}{c}
CH_3 \\
H_2C \quad\diagup\diagdown\quad CHCH_3 \\
| \qquad\qquad | \\
(CH_3)_2CH-HC \qquad CH_2 \\
\diagdown\quad\diagup \\
CO
\end{array}
\qquad (58)
$$
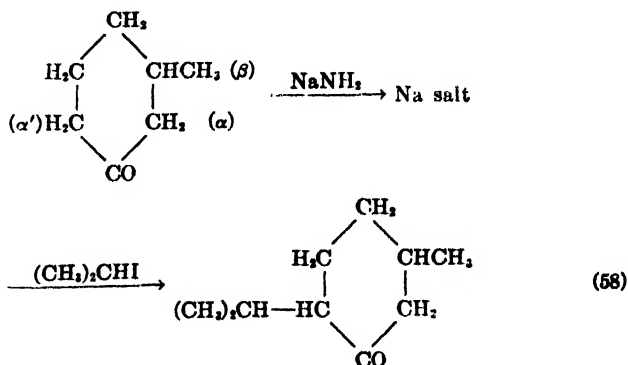
The second entering alkyl group goes to the α' position if the group already in this position (CH_3, etc.) is small. A large group, such as isopropyl (which is present in menthone), causes a second radical to enter into the α position, possibly because of steric influences (166, 167).

All of the three available α and α' hydrogens of menthone may be replaced by allyl but not by methyl groups (166). The final product of the methylation of β-methylcyclohexanone is α, α, α', α', β-pentamethylcyclohexanone (170). Owing to an unfortunate oversight, a number of important investigations of Cornubert, Haller and their associates, dealing with problems relating to the alkylation of substituted cyclopentanones and cyclohexanones, were not reviewed for this article. The references have been added to the proof (358, 359, 360, 361).

4. The alkylation of other ketones. Because of the limitations of space, it will not be possible to mention more than a few of the many other ketones that have been alkylated with the use of sodium amide.

Haller and Benoist (205) have prepared the methyl, benzyl, and allyl derivatives of benzoyltrimethylene, of the typical constitution,

$$C_6H_5-CO-C(R)-CH_2$$
$$\diagdown \diagup$$
$$CH_2$$
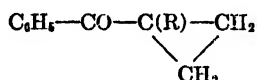
by treating benzoyltrimethylene with pure sodium amide in dry benzene, and then with the appropriate alkyl halide. Moist sodium amide or moist benzene favors the scission of the ketone into benzamide and a substituted trimethylene.

Godchot and Cauquil (154) have methylated cyclooctanone with sodium amide and methyl iodide, while Ruzicka, Stoll, and Schinz (295) have methylated cyclopentadecanone in a similar fashion.

Maxim (257) has extended the method of Haller to the synthesis of furanic ketones of the types,

$$C_4H_3O \cdot CHRCHR' \; COC_6H_5 \text{ and } C_4H_3O \cdot CHRCR'R'' \cdot COC_6H_5$$
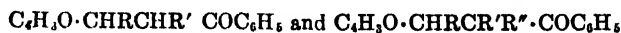
where the radicals R' and R'' are aliphatic and R is either aliphatic or aromatic.

C'. The preparation of acetylenic carbinols

Ruzicka, Rupe, and their coworkers (293, 294, 288, 289, 290) have found that acetylenic carbinols are easily formed by treat-

ing ketones with acetylene in the presence of sodium or sodium amide, the reaction following the type equation

$$(CH_3)_2CHCH_2CH_2CH_2COCH_3 \xrightarrow[C_2H_2]{NaNH_2} (CH_3)_2CH_2CH_2CH_2C{\overset{\displaystyle OH}{\underset{\displaystyle C\equiv CH}{\diagdown\diagup}}}CH_3 \quad (59)$$
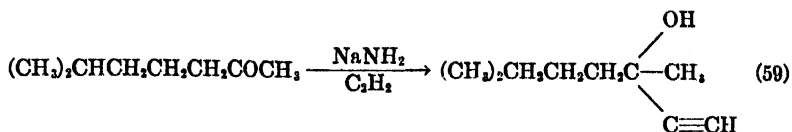
This synthesis was discovered by Nef (272), and later extended by many workers, whose investigations are reviewed in an article by Hess and Munderloh (220). It is of course possible first to form the sodium salt of acetylene by the action of sodium or sodium amide on acetylene, and then allow this to react with a ketone.

Heated with an excess of strong formic acid, the acetylenic carbinols are isomerized to unsaturated aldehydes in the manner of the equation

$$\overset{\displaystyle R\diagdown}{\underset{\displaystyle R\diagup}{}}C(OH)C\equiv CH \rightarrow \overset{\displaystyle R\diagdown}{\underset{\displaystyle R\diagup}{}}C{=}CH{-}CHO \quad (60)$$
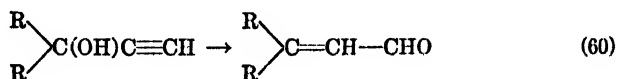
Ruzicka and Fornasir (293) have converted methylheptenone into linalool, while Wouseng (352a) has prepared methyl-*tertiary*-butylethinylcarbinol and a number of related substances in very good yield.

$$(CH_3)_3C{-}CO{-}CH_3 \xrightarrow[C_2H_2]{NaNH_2} (CH_3)_3C{-}C{\overset{\displaystyle CH_3}{\underset{\displaystyle C\equiv CH}{\diagdown\diagup}}}OH \quad (61)$$
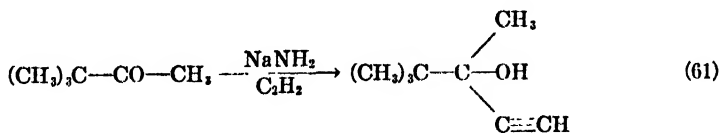
Pinacolone   Methyl-*tert.*-butylethinylcarbinol

Fischer and Löwenberg (121) have made use of these reactions in their synthesis of phytol.

According to German patents issued to Baeyer and Co. (27) sodium amide reacts with acetone in ether at low temperatures to form the sodium salt of the enol, apparently without any of the condensations which accompany the reaction at higher tem-

peratures.   Acetylene readily unites with this sodium salt in the following manner:

$$CH_3C(ONa) = CH_2 + C_2H_2 = (CH_3)_2C(OH)C \equiv CH \text{ (as the sodium salt) \quad (62)}$$
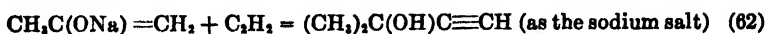
Reduction of this acetylenic carbinol gives 3-methylbutene-1-ol-3, $(CH_3)_2CH(OH)CH=CH_2$, which passes into isoprene, $CH_2=C(CH_3)CH=CH_2$, by the loss of a molecule of water. Several modifications of this synthesis are described in the patents referred to.

D. The scission of ketones by means of sodium amide

1. Decomposition of diaryl ketones.   In the course of investigations concerning the condensation of benzene solutions of certain diaryl ketones with sodium camphor, Haller and Bauer (170a) observed that the water used for the hydrolysis of the reaction mixture contained aromatic acids and their amides, while the expected condensation products remained dissolved in the hydrocarbon layer.   Subsequently, it was shown that the acids and acid amides were formed by the action of sodium amide upon the diaryl ketone, benzophenone thus decomposing into benzamide and benzene, in accordance with the equations

$$(C_6H_5)_2CO + NaNH_2 = (C_6H_5)_2C(NH_2)(ONa) \qquad (63)$$

$$(C_6H_5)_2C(NH_2)(ONa) + H_2O = C_6H_5CONH_2 + C_6H_6 + NaOH \qquad (64)$$
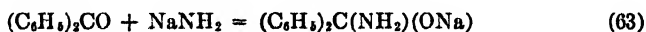
The first product of the action of sodium amide on benzophenone is assumed to be the addition compound on the right side of equation 63 (however, see reference 312).   This is converted by hydrolysis into benzamide and benzene (equation 64).   The alkaline wash waters from the precipitate of benzamide always contain a little sodium benzoate, resulting from the hydrolysis of the benzamide.   3,4-Xylyl phenyl ketone similarly is converted to approximately equal amounts of xylenic amide and benzamide, the scission therefore taking place in both of the possible ways, as shown by the following equations (252).

$$3,4\text{-}(CH_3)_2C_6H_3\text{—CO—}C_6H_5 \begin{cases} \xrightarrow{\ \ NaNH_2\ \ } 3,4\text{-}(CH_3)_2C_6H_3CONH_2\text{-}1 + C_6H_6 \\ \xrightarrow{\ \ NaNH_2\ \ } C_6H_5CONH_2 + o\text{-}(CH_3)_2C_6H_4 \end{cases} \qquad (65)$$
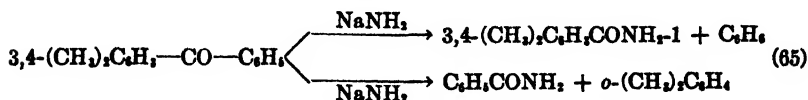
p-Tolyl phenyl ketone is split by sodium amide under the same conditions into benzamide and p-toluamide, while anisyl phenyl ketone yields benzamide and anisamide (170a).

The reaction expressed by equations 63, 64, and 65 appears to be general for all aromatic ketones, as well as for many of the mixed aliphatic-aromatic ketones, as will be seen later. The decomposition of benzophenone by fused potassium hydroxide follows a similar course, yielding benzene and potassium benzoate (80a, 108a).

Schönberg (312) extended these observations of Haller and determined a series representing the relative affinities of organic radicals for the carbonyl group of a ketone. In the reaction,

$$R—CO—R' + NaNH_2 = RCONHNa + R'H \qquad (66)$$

the radical R', eliminated as hydrocarbon, has a smaller relative affinity for the carbonyl group than R. The following order has been established. p-Anisyl > β-naphthyl > p-diphenylyl > phenyl > p-chlorophenyl > p-bromophenyl > m-chlorophenyl > m-bromophenyl. The dimethyl-p-aminophenyl radical has a greater, and the thienyl and triphenylmethyl radicals lower "affinities" than phenyl. In carrying out these reactions, the ketones, dissolved in benzene or toluene, were heated for several hours with sodium amide, the mixture cooled and hydrolyzed, the acid amide alone generally being the only reaction product determined. Since a mixture of amides is often obtained, the one found in least amount contains the radical of least "affinity" (i.e., more of the hydrocarbon containing this radical has been produced). It is interesting to note that in these experiments sodium amide has very little effect on the nuclear halogen.

Recently, de Cuester (78) has questioned the validity of Schönberg's method for determining relative affinities, or bond strengths, in that the course of these elimination reactions was found to depend upon the reagent used. Of fifty-seven ketone scissions described in the literature, fourteen are in agreement with Schönberg's theory, thirty-four in disagreement, and nine inconclusive. de Cuester himself has split twelve asymmetric diaryl ketones by at least two different methods, finding that four

conformed with the theory, five were in disagreement, and three were inconclusive. It is concluded that this reaction does not afford a sure method of measuring affinities.

2. The scission of trialkylacetophenones and trialkylacetonaphthones. Haller, Bauer, Ramart, Dumesnil and others (178, 3, 283, 112, 179) have decomposed trialkylacetophenones by means of sodium amide, in accordance with the general equation

$$C_6H_5—CO—CRR'R'' + NaNH_2 = C_6H_6 + RR'R''CONHNa \qquad (67)$$
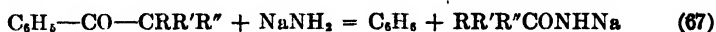
the reactions taking place in boiling benzene, toluene, or xylene, depending upon the resistance of the ketone. Occasionally, as when the benzyl, *p*-methylbenzyl, benzohydryl, or ethylphenylcarbinyl [$(C_2H_5)(C_6H_5)CH—$] radicals are among those that have been introduced into the methyl group of acetophenone, the scission partially takes place in the reverse sense, with the formation of a branched chain hydrocarbon and benzamide.

$$C_6H_5—CO—CRR'R'' + NaNH_2 = C_6H_5CONHNa + RR'R''CH \qquad (68)$$
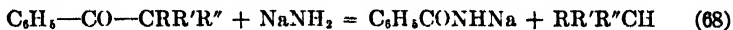
Thus, benzyldialkylacetophenones give benzene and benzyldialkylacetamides, as well as a branched chain hydrocarbon containing a benzyl group, according to both of the possible modes of decomposition represented by equations 67 and 68. It may be remarked that the reaction proceeds the more in accordance with equation 68 the heavier the radicals R and R'. Under favorable conditions, some branched chain hydrocarbons, as well as the more complex acid amides may best be synthesized in this manner.

As an illustration of this type of reaction, a solution of methylethylbenzylacetophenone, $(CH_3)(C_2H_5)(C_6H_5CH_2)C \cdot COC_6H_5$, was heated with four equivalents of sodium amide in xylene to about 140°C., where a vigorous reaction occurred, making necessary the cooling of the containing vessel. After the first reaction was over, the contents of the flask were refluxed for six hours, then cooled and hydrolyzed with water. Methylethylbenzylacetamide was obtained in 30 per cent yield, together with a smaller quantity of 2-benzylbutane (112a).

α,α-Dimethyl-β,β-diphenylpropiophenone is scarcely attacked by an excess of sodium amide in benzene or toluene, although re-

action does take place in boiling xylene. α,α-Diphenyl-β-methyl-propane and β,β-diphenyl-α,α-dimethylpropionamide are formed approximately to the same extent, in accordance with the equations

$$(C_6H_5)_3CHC(CH_3)_2COC_6H_5 \begin{cases} \xrightarrow{\quad NaNH_2 \quad} C_6H_5CONHNa + (C_6H_5)_3CHCH(CH_3)_2 \\ \xrightarrow{\quad NaNH_2 \quad} C_6H_6 + (C_6H_5)_3CHC(CH_3)_2CONH_2 \end{cases} \quad (69)$$
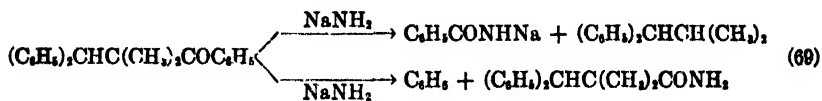
At the same time a fair quantity of sym-tetraphenylethane, $(C_6H_5)_2CHCH(C_6H_5)_2$, is obtained as a by-product. The manner in which it is formed is not clearly understood (3a).

The α-trialkylacetonaphthones normally decompose into tri-substituted acetamides (RR'R''CCONH$_2$) and naphthalene, while the β-isomers usually undergo the other method of scission with the production of trialkylmethanes and β-naphthoamide (254, 340).

3. The scission of hexaalkylacetones. Pentamethylethylacetone is decomposed by sodium amide in both possible ways to give pivalic acid amide, 2-methylbutane, the amide of dimethyl-ethylacetic acid, and isobutane (178).

$$\underset{\begin{subarray}{c} | \\ (CH_3)_3C-CO-C(CH_3)_2 \end{subarray}}{\overset{C_2H_5}{}} + NaNH_2 = (CH_3)_3CCONH_2 + (CH_3)_2CHCH_2CH_3$$
$$(70)$$
$$\text{or} \quad (CH_3)_2(C_2H_5)CCONH_2 + (CH_3)_3CHCH_3$$
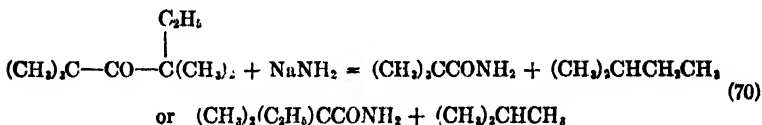
With ketones of the structure R''R'RC—CO—CRR'R'' and R''R'RC—CO—CR$_3$ the reaction with sodium amide is far from being as general as it is with the trialkylacetophenones (178, 194). The scission proceeds with unsymmetrically substituted ketones in both of the possible directions (cf. equation 70), but certain symmetrical ketones do not react at all with sodium amide. In the latter case, where decomposition does take place, only two products can be formed instead of four. Hexaethylacetone and $\alpha,\alpha,\alpha',\alpha'$-tetramethylisovalerone thus will not react with sodium amide; pentamethylethylacetone decomposes in the manner described above (equation 70); α,α',-dibenzyl-$\alpha,\alpha,\alpha',\alpha'$-tetra-methylacetone decomposes only into the amide of benzyldimethyl-acetic acid and dimethylbenzylmethane.

4. The scission and decomposition of diketones. Diketones similar to 2,6-dibenzoyl-2,6-dimethylheptane are decomposed by sodium amide (196) in accordance with the type equation

$$C_6H_5COC(CH_3)_2\!-\!CH_2CH_2CH_2\!-\!C(CH_3)_2COC_6H_5 \xrightarrow{\text{NaNH}_2}$$

$$\text{(70)}$$

$$NH_2COC(CH_3)_2\!-\!CH_2CH_2CH_2\!-\!C(CH_3)_2CONH_2 + 2C_6H_6$$

$$\alpha, \alpha, \alpha', \alpha'\text{-Tetramethylpimelamide}$$
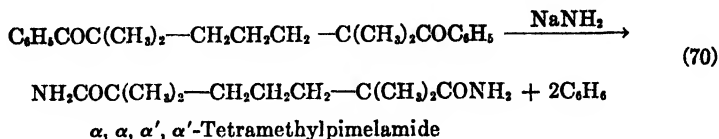
to give amides of dibasic acids, as would be predicted from the known method of scission of the trialkylacetophenones.

The complex diketones of Dumesnil (111) are ruptured according to the equation

$$C_6H_4[CH_2C(CH_3)_2COC_6H_5]_2 \ (o, m, \text{ or } p) \xrightarrow[\text{boiling xylene}]{\text{NaNH}_2}$$

$$C_6H_4[CH_2C(CH_3)_2CONH_2]_2 + 2C_6H_6 \qquad \text{(72)}$$
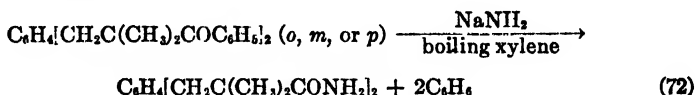
Kasiwagi (229) heated a toluene solution of benzil with sodium amide and obtained a good yield of benzilic acid from the products of hydrolysis of the reaction mixture. Unfortunately, the sodium hydroxide formed in the hydrolysis may have aided the rearrangement of benzil to benzilic acid, although it is certain that sodium amide alone would have sufficed. Haller (162) had previously published a brief note concerning the formation of benzilic acid from sodium amide and benzil.

5. The scission of cyclic ketones. Ketones in which the carbon of the carbonyl group is part of a ring system are split by sodium amide in the expected manner, with the formation of but a single product. Fluorenone is thus converted in almost quantitative yield to diphenyl-*o*-carboxylic acid amide (170a), as expressed by the equation

$$\begin{array}{c} C_6H_4 \\ | \quad\quad\; \rangle C\!=\!O + NaNH_2 = C_6H_5\!-\!C_6H_4CONHNa \ (o) \qquad \text{(71)} \\ C_6H_4 \end{array}$$
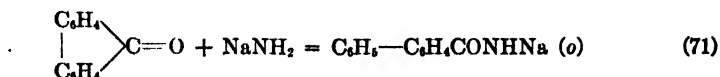
2,2-Dimethylindanone, under approximately the same conditions, is changed to α,α-dimethylhydrocinnamamide (184).

$$C_6H_4 \underset{\displaystyle CO}{\overset{\displaystyle CH_2}{\Big\langle\;\Big\rangle}} C(CH_3)_2 + NaNH_2 = C_6H_5CH_2C(CH_3)_2CONHNa \qquad \text{(72)}$$
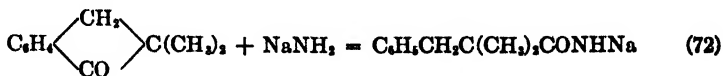
Tetraalkylcyclopentanones are decomposed by sodium amide with the opening of the ring. Thus, $\alpha,\alpha,\alpha',\alpha'$-tetramethylcyclopentanone is broken down into 2,2,5-trimethylcaproamide (210; cf. 17)

$$
\begin{array}{c}
\text{CH}_2\text{—C(CH}_3)_2 \\
\Big| \qquad\qquad \diagdown \text{CO} + \text{NaNH}_2 = (\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{C(CH}_3)_2\text{CONHNa} \qquad (73) \\
\text{CH}_2\text{—C(CH}_3)_2
\end{array}
$$
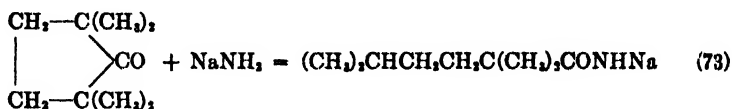
while $\alpha,\alpha,\alpha',\alpha',\beta$-pentamethylcyclopentanone is cleaved in both of the theoretically possible ways.

$$
\begin{array}{c}
\text{CH}_3 \qquad\qquad\qquad \nearrow \text{NH}_2\text{COC(CH}_3)_2\text{CH}_2\text{CH(CH}_3)\text{CH(CH}_3)_2 \\
\Big| \qquad\qquad\qquad \nearrow \\
\text{CH—C(CH}_3)_2 \nearrow \\
\qquad\qquad \diagdown \text{CO} \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (74) \\
\text{CH}_3\text{—C(CH}_3)_2 \diagdown \\
\qquad\qquad\qquad\qquad \searrow \\
\qquad\qquad\qquad \text{NH}_2\text{COC(CH}_3)_2\text{CH(CH}_3)\text{CH}_2\text{CH(CH}_3)_2
\end{array}
$$
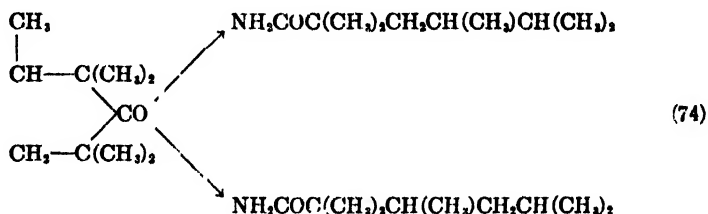
Other unsymmetrically substituted cyclopentanones are ruptured in the manner of equation 74.

Fenchone and camphor each contain two cyclopentane rings, in one of which there is a carbonyl group. Sodium amide should therefore split these ketones in accordance with one of the equations (71 to 74) above. Semmler (317) has indeed shown that fenchone is changed into fencholamide in the sense of the equation

$$
\begin{array}{c}
\text{CH} \qquad\qquad\qquad\qquad\qquad \text{CH—CH(CH}_3)_2 \\
\diagup \Big| \diagdown \qquad\qquad\qquad\qquad\qquad \diagup \qquad \diagdown \\
\text{H}_3\text{C} \quad\Big|\quad \text{C(CH}_3)_2 \quad\xrightarrow{\text{NaNH}_2}\quad \text{H}_3\text{C} \qquad \text{CH}_3 \\
\Big| \quad \text{CH}_2\Big| \qquad\qquad\qquad\qquad\qquad \Big| \qquad\qquad \Big| \\
\text{H}_2\text{C} \quad\Big|\quad \text{CO} \qquad\qquad\qquad \text{H}_2\text{C——C—CONHNa} \qquad (75) \\
\diagdown\Big|\diagup \qquad\qquad\qquad\qquad\qquad\qquad\qquad \Big| \\
\text{C} \qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{CH}_3 \\
\Big| \\
\text{CH}_3
\end{array}
$$
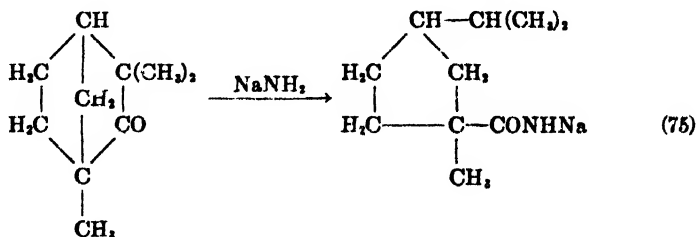
Haller and Bauer (182) and Haller and Louvrier (213a) have shown that the dialkylcamphors, prepared by the alkylation of camphor with sodium amide and alkyl iodides, further react with an excess of the former reagent under a heated hydrocarbon oil to

form dialkylcampholamides. The reaction is expressed by the following equation

$$
\underset{\text{C(CH}_3\text{)}}{\overset{\text{CH}}{\underset{\parallel}{\underset{\text{H}_2\text{C}}{\bigg|}}}}\; \text{CH}_3\text{CCH}_3 \;\underset{\text{C=O}}{\overset{\text{CR}_2}{\bigg|}} \quad \xrightarrow{\text{NaNH}_2} \quad \text{(76)}
$$

(CH—CHR₂ / CH₃C—CH₃ / C(CH₃)CONHNa structure)
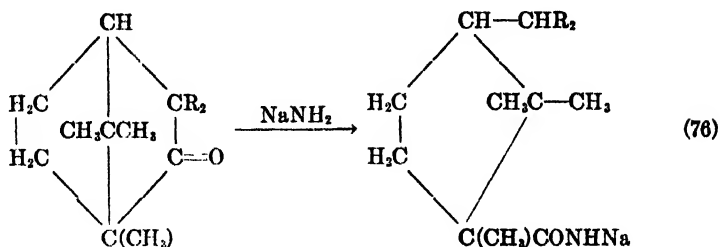
Nametkin (271) has similarly decomposed β-methylcamphenilone into β-methylcamphenylic acid amide.

Tetrasubstituted cyclohexanones fail to react appreciably with sodium amide, even after long heating in boiling xylene (163).

Benzoyltrimethylene is cleaved by moist sodium amide under benzene to benzamide and trimethylene (206), while benzoyl-benzyltrimethylene

$$
\underset{\text{CH}_2}{\overset{\text{C}_6\text{H}_5\text{COC(CH}_2\text{C}_6\text{H}_5)\text{CH}_2}{\diagdown \diagup}}
$$
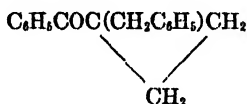
is split into benzene and the amide of benzyltrimethylenecar-boxylic acid (207).

Benzoyl-1-phenyl-2- Δ₁-cyclopentene and related compounds break up in both of the possible ways (17).

$$
\underset{\text{CH}_2\text{---C---COC}_6\text{H}_5}{\overset{\text{CH}_2\text{---CH}_2}{\diagup}}\!\!\!>\!\!\text{C---C}_6\text{H}_5 \begin{cases} \nearrow & \text{CH}_2\text{---CH}_2 \\ & \diagup\text{C---C}_6\text{H}_5 + \text{C}_6\text{H}_6 \\ & \text{CH}_2\text{---C---CONH}_2 \\ \searrow & \text{CH}_2\text{---CH} \\ & \diagup\text{C- -C}_6\text{H}_5 + \text{C}_6\text{H}_5\text{CONH}_2 \\ & \text{CH}_2\text{---CH} \end{cases} \quad \text{(77)}
$$
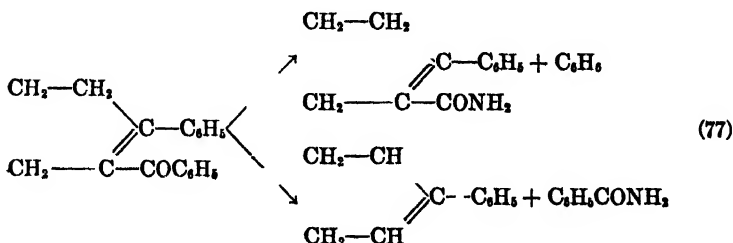
Sachs (299) obtained diphenyl by heating phenanthrenequinone with fused sodium amide.

E. Condensation reactions of the allylalkylacetophenones and acetonaphthones

The unsaturated ketones named in the heading are condensed to substituted pyrrolidones, in accordance with the type equation below.

$$C_6H_5CO—C \underset{CH_2CH=CH_2}{\overset{(CH_3)_2}{\big<}} \xrightarrow{NaNH_2} \underset{CO———NH}{\overset{(CH_3)_2C—CH_2—CH—CH_3}{|}} + C_6H_6 \quad (78)$$

3 3,5-Trimethylpyrrolidone
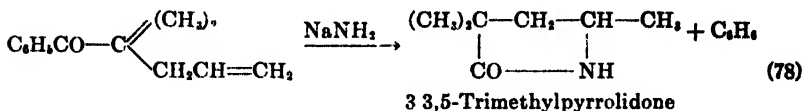
This apparently complex reaction was explained by Haller, who assumed that sodium amide first cleaves the ketone to benzene and the sodium salt of an acid amide of the composition, $NaNHCOC(CH_3)_2CH_2CH=CH_2$. The —NH— portion of the molecule adds to the double bond of the allyl group to form

$$\underset{CO———N—Na}{\overset{(CH_3)_2C—CH_2—CH—CH_3}{|}}$$
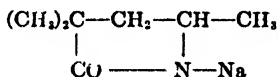
and this passes by hydrolysis into the substituted pyrrolidone on the right side of equation 78 (201, 203, 213b).

Dimethylallylacetonaphthone (α) either yields allyldimethylacetamide and naphthalene, decomposing therefore in the manner of a trialkylacetophenone, or else it yields naphthalene and trimethylpyrrolidone, as in the reaction of equation 78.

F. Cyclization of ketones by sodium amide

Sodium amide will cause many ketones, acids, and acid amides to lose water intramolecularly with the formation of cyclic compounds. The synthesis of indoxyl from phenylglycine and of substituted indoles from acyl derivatives of o-toluidine are illustrations of this type of reaction, but a further discussion will be reserved for a later section of this review.

The conversion of a ketone to a cyclic compound by means of sodium amide is usually the result of a crotonaldehyde type reaction involving the loss of water between the oxygen of carbonyl and two hydrogens of a methyl or methylene group favorably situated spatially elsewhere within the molecule.

Bauer (14) has thus found that 1,6- and 1,7-diketones are converted to acyl derivatives of cyclopentene and cyclohexene, respectively, in the manner of the type equation

$$
\begin{array}{ll}
\text{CH}_2\text{CH}_2\text{COC}_6\text{H}_5 & \text{CH}_2\text{CH}_2 \\
\quad\quad\quad \dfrac{+\ \text{NaNH}_2}{-\ \text{H}_2\text{O}} & \qquad\qquad \diagdown \\
& \qquad\qquad\quad > \text{C---C}_6\text{H}_5 \\
\text{CH}_2\text{CH}_2\text{COC}_6\text{H}_5 & \text{CH}_2\text{C---COC}_6\text{H}_5
\end{array}
$$

$$
\begin{array}{ll}
& \text{CH}_2\text{CH} \\
\text{and} & \qquad\quad \diagdown \\
& \qquad\qquad > \text{C---C}_6\text{H}_5 \\
& \text{CH}_2\text{CH---COC}_6\text{H}_5
\end{array}
$$

(77a)
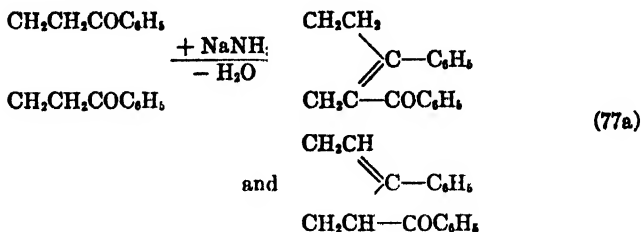
The second compound is formed from the first by a prototropic (i.e., a tautomeric) change (223).

XII. ACIDS AND THEIR DERIVATIVES, EXCLUSIVE OF ESTERS

A. Acids

It has been the general experience of a number of investigators that sodium or potassium amide react with substances that are recognized as acids of the water system to form alkali metal salts. Literature references to such evident facts are not necessary. R. A. Fulton (145; cf. 319), working in the laboratories of Stanford University, has observed the formation of methane when sodium acetate is fused with sodium amide, the reaction resembling the well-known method for the preparation of this gas from sodium acetate and soda lime.

Staudinger and Meyer (319) state that potassium diphenylacetate is converted by heated potassium amide to the dipotassium salt of diphenylmethylenecarbonic acid, in accordance with the equation

$$(\text{C}_6\text{H}_5)_2\text{CHCOOK} + \text{KNH}_2 = (\text{C}_6\text{H}_5)_2\text{CH(OK)}_2\text{NH}_2 =$$
$$(\text{C}_6\text{H}_5)_2\text{C}\!=\!\text{C(OK)}_2 + \text{NH}_3 \tag{79}$$
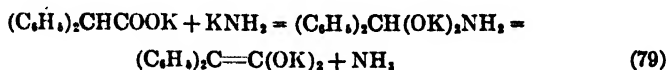
Bauer (22, 18a) treated δ-benzoylvaleric acid, $\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{-CH}_2\text{CH}_2\text{COOH}$, with sodium amide and obtained the cyclic compound, α-benzoylcyclopentanone.

CH$_2$——CH$_2$

CH$_2$ CHCOC$_6$H$_5$

CO
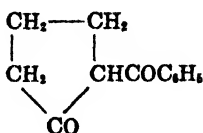
B. Acid amides and proteins

Franklin and his coworkers (126, 136, 128, 129) have shown
that the acid amides, $RCONH_2$, are mixed acids of the water and
ammonia systems, and as such should show the properties of
acids, at least in liquid ammonia solution. While it is true that
only a few acid amides show well defined acidic properties in
water (cf. 256), it is equally true that every acid amide examined
by Franklin and his students forms salts in liquid ammonia with
bases of the type of sodium or potassium amide. Furthermore,
these salts may generally be obtained in definite crystalline form,
and therefore in an analytically pure state. In most cases they
are hydrolyzed by water to a base of the water system and an acid
amide, a reminder of the fact that the ionic product of water
($H^+ \times OH^-$) is much greater than that of ammonia, ($H^+ \times
NH_2^-$) (140, 134, 125 footnote).

As an illustration, Franklin and Stafford (136), and Miss R. V.
Fulton (148) prepared monopotassium acetamide by bringing
together liquid ammonia solutions of potassium amide and acet-
amide, the reaction proceeding rapidly in accordance with the
equation

$$KNH_2 + CH_3CONH_2 = CH_3CONHK + NH_3 \qquad (80)$$

The salt is very soluble in liquid ammonia at room temperature,
but can be crystallized at $-40°C$. from a solution of proper con-
centration. It is perhaps needless to say that, as far as the evi-
dence goes, potassium acetamide may as well be represented by
the formula, $CH_3C(OK)=NH$. Since the salt is ionic in nature,
it may be meaningless to attempt to distinguish between the two
structures. Potassium acetamide is decomposed by hydrolysis
into acetamide and potassium hydroxide.

$$CH_3CONHK + H_2O = CH_3CONH_2 + KOH \qquad (81)$$

The acetamide, under favorable conditions, may of course be further hydrolyzed to acetic acid.

Franklin, Franklin and Stafford (122, 102, 136, 40), and Miss Fulton (148) prepared the sodium and potassium salts of a number of acid amides by the general reaction illustrated in equation 80. Among these were the monopotassium salts of phenylacetamide, benzamide, urea, benzenesulfonamide, m-methoxybenzenesulfonamide, saccharin, propionamide, butyramide, valeramide, capramide, palmitamide, and the dipotassium salts of benzamide, benzenesulfonamide, m-methoxybenzenesulfonamide, and urea.

The pioneer work of Franklin and Stafford was not the first recorded preparation of metallic salts of the acid amides. Titherley (331) treated formamide, acetamide, propionamide, and benzamide with sodium amide under boiling benzene, and isolated the monosodium salts of each of these in a fairly pure condition. Similar salts had been made before the date of publication of Titherley's article, but without the use of metallic amides.

Since the paper of Franklin and Stafford, a number of articles have been written upon the subject of the acid amides and their salts, but it would unduly lengthen this review to include more than the references (122, 102, 40, 148, 136). In reading some of the older articles, it should be borne in mind that the acid amides are mixed aquoammonocarboxylic acids (carboxyazylic acids) and not ammono acids, as has often been incorrectly stated.

Miss R. V. Fulton (148) prepared monopotassium formamide, HCONHK, by the action of a liquid ammonia solution of potassium amide on an excess of formamide. If, conversely, more than one molecular proportion of potassium amide is used in this preparation, at room temperatures, hydrogen is evolved in close agreement with the equation

$$HCONHK = H_2 + KNCO \qquad (82)$$

Potassium cyanate, a salt of a mixed aquoammonocarbonic acid, may readily be isolated from the reaction mixture.

A related, although not strictly comparable, reaction of the water system is the conversion of sodium formate into hydrogen and sodium oxalate, by the action of an excess of heated sodium

hydroxide (155, 115, 233). If a mixed aquoammonooxalate is formed in Miss Fulton's reaction, it is converted under the influence of the excess of potassium amide, to potassium cyanate and hydrogen.

The potassium salts of the higher fatty acid amides (acetamide to n-caproamide) when heated by themselves, and therefore in the absence of excess potassium amide, decompose in two different ways: (1) to give a hydrocarbon and a cyanate,

$$RCONHK = KNCO + RH \qquad (83)$$

a reaction closely akin to the preparation of methane by heating sodium acetate with soda lime, and (2) to give a nitrile and potassium hydroxide.

$$RCONHK = KOH + RCN \qquad (84)$$

In the latter decomposition, the acid amide has merely been dehydrated to an acid anammonide, or nitrile. Specifically, potassium n-caproamide heated to 220°C., decomposes in accordance with equations 83 and 84 to the extent of about 28 per cent and 72 per cent, respectively. The purity of the pentane formed in reaction 83 was not determined.

R. A. Fulton (145) treated a series of the lower aliphatic acid amides with an excess of fused potassium amide, obtaining hydrocarbons and dipotassium cyanamide, a salt of an ammonocarbonic acid.

$$RCONH_2 + 3KNH_2 = RH + K_2CN_2 + KOH + 2NH_3 \qquad (85)$$

The higher hydrocarbons (i.e., above ethane) that would be anticipated in the reaction of equation 85 are cracked to hydrocarbons of lower carbon content and hydrogen by the fused amide.

McChesney and Miller (255) have observed that proteins are partially ammonolyzed by solutions of sodium and potassium amide in liquid ammonia, the latter ammono base being the more effective. As a rule, it is advisable to heat the protein with the alkali metal amide and ammonia to about 110–120°C. for two or three days, but even then the ammonolysis is incomplete. The extent of the decomposition is found by determining the ratio of amide nitrogen to total nitrogen in the reaction product. Under the most favorable conditions, in an experiment when silk was

heated with sodium amide and ammonia at 120°C. for four days, this ratio was only 0.306.

C. The indigo synthesis

Sodium amide has long been used in the conversion of phenylglycine to indoxyl, an intermediate in the commercial synthesis of indigo. The complete equations for the preparation of this important dyestuff from aniline are the following:

$$C_6H_5NH_2 \begin{array}{c} + CH_2ClCOOH \\ \hline - HCl \end{array}$$

$$\begin{array}{c} HO \\ \diagdown \\ C{=}O \\ | \\ CH_2 \\ | \\ NH \end{array} \xrightarrow[NaNH_2]{- H_2O} \begin{array}{c} CO \\ \diagdown \\ CH_2 \\ / \\ NH \end{array} \quad (86)$$

Indoxyl

$$C_6H_4 \begin{array}{c} CO \\ \diagdown \\ / \\ NH \end{array} C{=}C \begin{array}{c} CO \\ \diagdown \\ / \\ NH \end{array} C_6H_4 \xleftarrow{\quad O_2 \quad}$$

Indigo
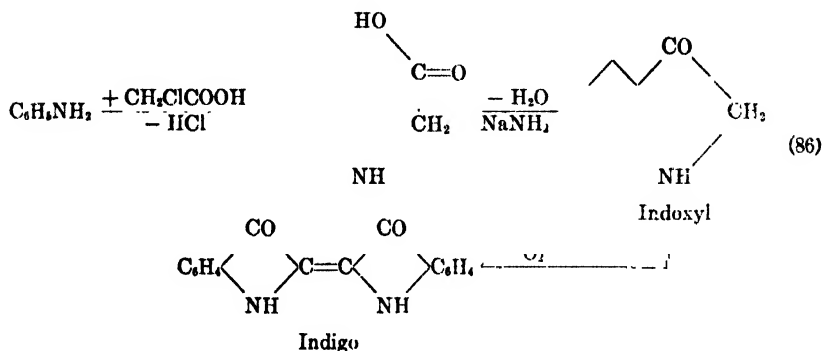
Rather unsatisfactory yields of indoxyl were obtained in the second stage of the reaction when fused alkali hydroxides were used to bring about the ring closure (2, 141), but sodium amide (151b), either alone or mixed with sodium hydroxide, has been of great advantage in making this process a commercial success. Many other intermediates of the type of phenylglycine have been converted to bicyclic ring systems by the use of sodium amide (222).

D. The preparation of substituted indoles

With the synthesis of indoxyl as a prototype, Verley (338) and Verley and Berdurvé (339) heated the acetyl derivative of o-toluidine with 2.5 parts of sodium amide at 250°C. and obtained α-methylindole in good yield, the reaction proceeding in accordance with the equation

$$C_6H_4 \begin{array}{c} CH_3 \\ \diagdown \\ / \\ NHCOCH_3 \end{array} \xrightarrow[NaNH_2]{- H_2O} C_6H_4 \begin{array}{c} CH \\ \diagdown \\ / \\ NH \end{array} C{-}CH_3 \quad (87)$$
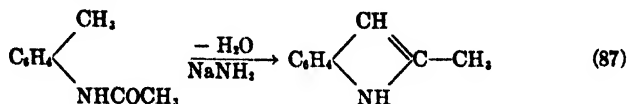
2-Ethyl-, 2-*n*-propyl-, and 2-isobutyl-indoles were synthesized in a like manner. Indole itself was prepared by heating form-*o*-toluide with sodium amide and kieselguhr in the presence of an inert liquid.

E. Acid chlorides

Baumert and Landolt (25) state that dibenzamide as well as benzamide is formed by the action of sodium or potassium amide on benzoyl chloride, in the sense of the following equation, in which the formation of dibenzamide is illustrated.

$$2C_6H_5COCl + 3NaNH_2 = (C_6H_5CO)_2N \cdot Na + 2NaCl + 2NH_3 \quad (88)$$

$$(C_6H_5CO)_2 N \cdot Na + H_2O = NaOH + (C_6H_5CO)_2NH$$
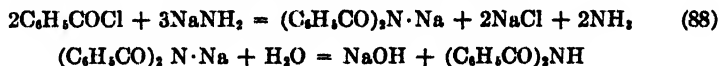
While sodium hydroxide and benzoyl chloride react to form sodium benzoate, sodium amide reacts to form also the sodium salt of a mixed aquoammonod*i*benzoic acid, a strict analogue of which in the water system alone is impossible. Undoubtedly the products obtained in the reaction of equation 88 will depend to a large extent upon experimental conditions.

Alexieff (5) prepared acetamide, isovaleramide, benzamide, and benzenesulfonamide by adding sodium amide to a solution of the corresponding acid chloride in benzene or xylene. Succinic and phthalic anhydrides are attacked much more slowly by sodium amide with the formation chiefly of salts of acids which contain one COOH and one CONH$_2$ group.

F. Nitriles and related compounds

1. The formation of amidines, of salts, and of cyanphenins and cyanalkines from nitriles. Cornell (103, 130), working under Dr. E. C. Franklin, advanced the hypothesis that the acid nitriles are anammonides of "carbazylic" acids of the ammonia system, since they are related to a class of ammono acids, the acid amidines, in much the same manner that the familiar acid anhydrides of the water system are related to their parent acids.

$$2CH_3COOH - H_2O = (CH_3CO)_2O$$
$$CH_3C(\!=\!NH)NH_2 - NH_3 = CH_3CN \quad (89)$$
$$\text{Acetamidine} \qquad \text{Acetonitrile}$$
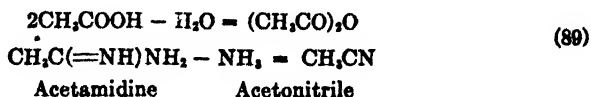
The fact that nitrogen is trivalent while oxygen is divalent makes it possible to prepare an acid anammonide by loss of ammonia from a single molecule of ammonoacetic acid.

With the relationship of the nitriles to the acids of the ammonia system in mind, Franklin and Cornell reasoned that it should be possible to prepare salts of the amidines by treating liquid ammonia solutions of the nitriles with potassium or sodium amide. These reactions were indeed found to proceed very rapidly in liquid ammonia at room temperatures, in accordance with the equation

$$RCN + KNH_2 = RC(=NH)NHK \tag{90}$$
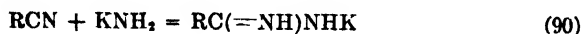
Cornell thus prepared alkali metal salts of acetamidine, propionamidine, isocaproamidine, palmitamidine, benzamidine, butyramidine, valeramidine, succinamidine, and p-toluamidine. In some cases, the free amidine was isolated from the products of the water hydrolysis of its salt.

Previous to the publication of Cornell's article, Mlle. Ramart (282) refluxed solutions of n-valeronitrile, caprylonitrile, and diethylacetonitrile with sodium amide in ether, forming sodium salts that were not isolated. Addition of benzyl chloride to the reaction mixtures, with a subsequent working up of the products, gave α-benzyl derivatives of the nitriles. One may assume for the time that the reaction follows the course,

$$RCH_2CN + NaNH_2 = RCHNaCN + NH_3 \tag{91}$$
$$RCHNaCN + C_6H_5CH_2Cl = RCH(CH_2C_6H_5)CN + NaCl$$
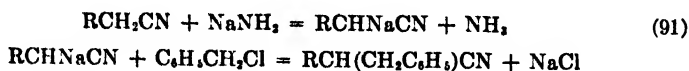
Quite recently, Ziegler and Ohlinger (354) have greatly extended the earlier work of Ramart, and have succeeded in developing a general method for the alkylation of aliphatic nitriles. In the course of their investigations, it was found that the higher nitriles react with a suspension of sodium amide in benzene at 60–70°C. to give the sodium salts of the acid amidines (compare equation 90), which were not isolated as such but were hydrolyzed to form the free amidines in good yield. In this fashion, Ziegler and Ohlinger prepared diethylacetamidine, diethylallylacetamidine, and triethylacetamidine.

Lithium salts of the aliphatic nitriles, presumably of the constitution, $R_2C(Li)CN$ or $R_2C=C=N$—Li, were readily prepared by the action of lithium diethylamide, $(C_2H_5)_2NLi$, upon the nitrile, diethylamine of course being the other reaction product. The lithium diethylamide was most readily made by adding diethylamine to an ethereal solution of lithium phenyl. Therefore, a small amount of a suitable secondary amine, in the presence of lithium phenyl, will serve as a catalyst for converting a large amount of a nitrile to its lithium salt. Addition of an alkyl halide to the solution of the lithium salt of the nitrile gave an α-alkyl derivative of the nitrile, in accordance with the equation

$$(C_2H_5)_2CLiCN + CH_2=CHCH_2Cl = LiCl + (C_2H_5)_2C(CH_2CH=CH_2)CN \quad (92)$$

A further improvement in this method consisted in the use of a very fine suspension of sodium amide in benzene, prepared by grinding these two substances together for several days in a ball mill. To lessen the formation of amidine, in accordance with equation 90, this suspension of sodium amide in benzene was refluxed for some time with a mixture of the alkyl halide and nitrile and then carefully hydrolyzed with water. Alkylated nitriles were isolated in good yield.

Among the nitriles that Ziegler and Ohlinger prepared are the following: diethylacetonitrile, diallylethylacetonitrile, dibenzylpropionitrile, diisopropylacetonitrile, diethylacetonitrile, and n-capronitrile, the latter being made by refluxing a mixture of acetonitrile, n-butyl bromide, and sodium amide in absolute ether. It is of interest that diethylacetonitrile was prepared by two methods: first, by heating a mixture of ethyl bromide, ether, and n-butyronitrile with sodium amide; and, second, in the same manner, except that the butyronitrile was replaced by half an equivalent of acetonitrile, which therefore was alkylated twice in the alpha position. Ziegler (357), who has recently patented this process, states that several of the nitriles can be hydrolyzed to acid amides which may prove of value as hypnotics.

Under altered conditions, sodium amide is reported to cause the trimerization of nitriles to cyanalkines or cyanphenins. E. von Meyer (262) has obtained these substances in good yield by

heating sodium amide with methyl, ethyl, benzyl, and phenyl cyanides. Unfortunately the original article is not available and it is not possible to state the conditions under which the reactions were carried out.

2. The action of highly heated or fused amides on the nitriles. Cornell (103) heated the potassium salts of a number of amidines with potassium amide and obtained hydrocarbons in accordance with the equation

$$RC(\!=\!NH)NHK + KNH_2 = RH + K_2NCN + NH_3 \qquad (93)$$
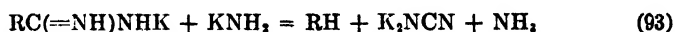
Previously, Miss R. V. Fulton (148) had carried out similar experiments. The reactions are analogous to the decomposition of sodium acetate by heated soda lime into methane and sodium carbonate, since dipotassium cyanamide is a potassium carbonate of the ammonia system (127).

Knowing that the higher hydrocarbons cannot be prepared in a pure state by the action of heated alkalis on the salts of the aquo fatty acids, R. A. Fulton and Bergstrom (146) passed a number of aliphatic nitriles through molten potassium amide. The potassium salt of the amidine, first formed (see equation 90), is at once decomposed into a mixture of hydrocarbon gases, in which the lower hydrocarbons predominate. Hydrogen is always present in the gaseous reaction products from the decomposition of the nitriles containing three or more carbon atoms.

Kirkish (231, 232) has found that phenyl, benzyl, *p*-tolyl, and *α*-naphthyl cyanides are decomposed by fused sodium amide into benzene, toluene and naphthalene, respectively, and disodium cyanamide. The yield of hydrocarbon is 30 to 60 per cent of the theoretical.

3. Phenylacetonitrile. Phenylacetonitrile, $C_6H_5CH_2CN$, presents a case of especial interest, since it does not form an amidine when treated with the alkali metal amides, because of the great reactivity of the hydrogen atoms of the methylene group. Instead, the reaction follows the course of the equation,

$$NaNH_2 + C_6H_5CH_2CN = NH_3 + C_6H_5CHNaCN \text{ (or } C_6H_5 \cdot CH\!=\!C\!=\!NNa) \qquad (94)$$
in ether or benzene
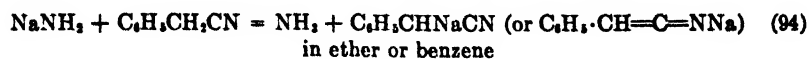
There is some question as to the structure of the sodium salt so formed, although most investigators seem to prefer the latter, or "nitride," formula (cf. also 286, 336).

Sodium phenylacetonitrile is converted by alkyl halides in ether solution into α-alkylated phenylacetonitriles, according to the equation,

$$C_6H_5CHNaCN + RX = C_6H_5CHRCN + NaX \qquad (95)$$
$$X = halogen$$

The α-alkylacetonitriles obtained in this reaction may again be alkylated, by a repetition of the processes represented by equations 94 and 95, to give $C_6H_5CRR'CN$ (51, 53, 54, 55, 199, 221, 282a, 283a, 285, 286, 337).

The sodium salt of phenylacetonitrile condenses very readily with suitable esters, aromatic acid halides, and ketones, in the manner of the following equations.

$$2C_6H_5CHNaCN + CH_2(COOC_2H_5)_2 = CH_2[COCH(C_6H_5)CN]_2 + \qquad (96)$$
$$2C_2H_5ONa \ (45, 49)$$

$$C_6H_5CHNaCN + C_6H_5CHO = C_6H_5CH=C(C_6H_5)CN + NaOH \ (52, 50) \qquad (97)$$
A little benzoic acid is formed at the same time.

$$C_6H_5COC_6H_5 + C_6H_5CHNaCN = (C_6H_5)_2C=C(C_6H_5)CN + \qquad (98)$$
$$NaOH \ (46, 47, 48)$$

$$C_6H_5COCl + C_6H_5CHNaCN = C_6H_5COCH(C_6H_5)CN + NaCl \ (45, 46) \qquad (99)$$
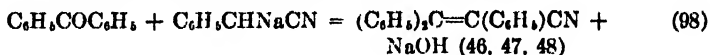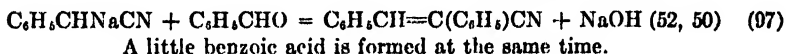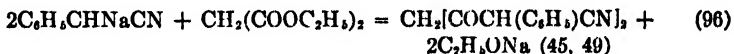
The illustrations that have been given are taken from the articles of Bodroux, who used sodium amide in preparing sodium phenylacetonitrile. This salt can also be made by the action of sodium on phenylacetonitrile and condensations of the latter can be effected without the previous preparation of its sodium derivative, provided the nitrile, the substance with which it is to condense, and an alcoholic solution of sodium ethylate are refluxed together. References to reactions in which sodium amide has not been used are omitted.

Cloke, Anderson, Lachmann, and Smith (101) successfully prepared cyclopropyl cyanide by adding a suspension of sodium amide in toluene to a solution of γ-chlorobutyronitrile in liquid ammonia. The reaction follows the equations

$$ClCH_2CH_2CH_2CN + NaNH_2 = NH_3 + ClCH_2CH_2CHNaCN$$

$$\text{(100)}$$

$$ClCH_2CH_2CHNaCN = NaCl + H_2C{-\!\!-\!\!-}CHCN$$
$$\diagdown\diagup$$
$$CH_2$$
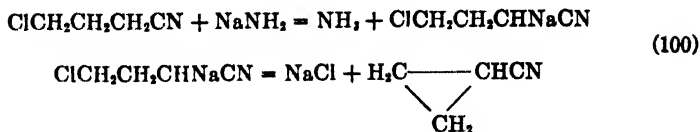
and consistently gives yields varying between 75 and 90 per cent of the theoretical. Omission of the liquid ammonia very definitely decreases the yield, while even less satisfactory results are obtained by using potassium hydroxide in place of sodium amide (206, 275, 100).

Using the same method, Knowles and Cloke (234) prepared 1-phenyl-1-cyanocyclopropane by treating a liquid ammonia solution of α-phenyl-γ-chlorobutyronitrile with sodium amide.

More simply, phenylacetonitrile was treated with 2 mole proportions of sodium amide in ether, the resulting sodium salt then reacting with ethylene chlorobromide, in the presence of the excess of sodium amide, to give 1-phenyl-1-cyanocyclopropane.

$$C_6H_5CH_2CN \xrightarrow{NaNH_2} C_6H_5CHNaCN \xrightarrow{ClCH_2CH_2Br} C_6H_5CHCN \xrightarrow{NaNH_2}$$
$$|$$
$$CH_2CH_2X$$

$$C_6H_5CNaCN \qquad\qquad C_6H_5{-}C{-}CN$$
$$| \qquad\qquad \xrightarrow{-NaX} \qquad \diagup\diagdown \qquad \text{(101)}$$
$$CH_2CH_2X \qquad\qquad CH_2{-} \; CH_2$$

$$X = Cl \text{ or } Br$$
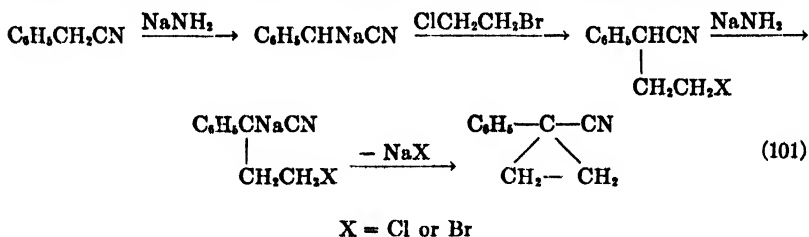
The first step in the reaction is an extension of the earlier work of Bodroux and Taboury (51, 55).

4. Hydrocyanic acid, the cyanides, isocyanides, and cyanogen. Hydrocyanic acid may be considered either as a nitrile of formic acid, H—CN (therefore a formic acid anammonide) or an ammonocarbonous acid, HN≕C (132). The reaction of this substance with potassium amide in liquid ammonia results in the formation of potassium cyanide to the exclusion of a salt of formamidine, HC(≕NH)NHK (a potassium ammonoformate) (103a).

Perret and Krawczynski (277) very recently have found that hydrocyanic acid gas reacts with sodium amide at temperatures between 150°C. and 250°C. to form a mixture of sodium cyanamide and sodium cyanide, the former arising from the reaction

$$NaNH_2 + HCN = H_2 + NCNHNa \qquad (102)$$
$$NCNHNa + excess \; NaNH_2 = NCNNa_2 + NH_3$$

It will be recalled that sodium cyanide has previously been reported to react with sodium amide to form disodium cyanamide (see Part I, reference 116).

Cornell (103a) has found that cyanogen reacts with a liquid ammonia solution of potassium amide to form potassium cyanide and cyanamide, in qualitative agreement with the equation

$$C_2N_2 + 3KNH_2 = K_2CN_2 + CNK + 2NH_3 \qquad (103)$$

Perret and Krawczynski (277) have made an extended investigation of the action of cyanogen gas on sodium amide in the absence of a solvent, and have observed that between 90°C. and 120°C. there is no reaction other than a polymerization of the cyanogen to paracyanogen. With an increase in the temperature (which may reach 350°C.) sodium cyanamide is formed, apparently as the primary product of the reaction, while variable quantities of cyanide are obtained at the same time.

$$NaNH_2 + (CN)_2 \; (or \; (CN)_x) = NaNHCN + HCN \qquad (104)$$
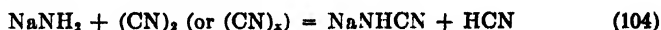
In the presence of an excess of sodium amide, it is probable that the monosodium cyanamide is converted to disodium cyanamide. Hydrocyanic acid is not liberated in the free state, since it reacts with an excess of heated sodium amide to form both sodium cyanide and sodium cyanamide (equation 102). The relative extent to which these reactions occur depends upon the experimental conditions. The reaction of Castner (Part I, reference 116)

$$NaNH_2 + NaCN = Na_2CN_2 + H_2 \qquad (105)$$
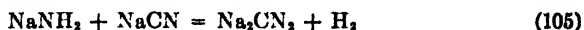
does not appear to be of importance in the present work, since it was found not to take place at temperatures up to 250°C., although hydrocyanic acid itself is stated to react with sodium amide in the manner of equation 102.

Franklin (132a) has shown that ethyl isocyanide reacts with potassium or sodium amide in liquid ammonia (at 80°C.) to form ethylamine (an ammono alcohol) and potassium or sodium cyanide.

$$C_2H_5NC + KNH_2 = C_2H_5NH_2 + KCN \qquad (106)$$

Therefore, ethyl isocyanide behaves as an ester of an ammono-carbonous acid, $HN\!\!=\!\!C$, undergoing saponification in the antici-pated manner. It is clear from the preceding paragraphs that the normal alkyl cyanides, or nitriles, cannot be considered as esters of hydrocyanic acid.

XIII. ESTERS

A. Esters not undergoing the Claisen condensation (exclusive of alkyl halides, etc.)

Sodium amide, a base of the ammonia system, should saponify an ester in one of the following ways:

$$RCOOR' + NaNH_2 = RCONHNa + R'OH \qquad (107)$$

yielding the sodium salt of an acid amide (mixed aquoammono acid) and an aquo alcohol, or

$$RCOOR' + NaNH_2 = RCOONa + R'NH_2 \qquad (108)$$

giving the sodium salt of an aquo acid and an amine (ammono alcohol). Experiment has shown that the first mode of decom-position generally predominates, if the sodium amide does not cause the ester to undergo condensation.

Titherley (333) examined the action of sodium amide on ben-zene solutions of a number of typical esters, and found that the reaction in the cold apparently first leads to the formation of an unstable addition compound,

$$RCOOR' + NaNH_2 = R - C \begin{cases} OR' \\ ONa \\ NH_2 \end{cases} \qquad (109)$$
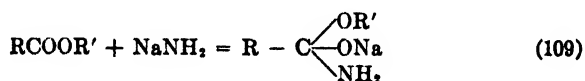
It will be recalled that the carbonyl group of an ester in many cases adds potassium or sodium hydroxide or the alkali metal alcoholates. Intermediate products of the type represented in equation 109 were observed in the reactions between sodium amide and esters of acetic, oxalic, and benzoic acids. The mode in which this addition compound decomposes depends upon the ester, as well as upon experimental conditions.

Ethyl, butyl, and amyl formates react with sodium amide in

benzene to give ammonia and sodium formate (333). The experiments are not described in detail sufficient to decide between the two alternatives: first, that the sodium formate is produced in accordance with equation 108, in which case an amine should likewise be formed; and, second, that the sodium formate is a secondary product resulting from the subsequent hydrolysis of formamide in alkaline solution (cf. equation 107).

Ethyl benzoate reacts slowly with sodium amide in warm benzene to form sodium benzamide, sodium benzoate, and sodium ethylate, the relative proportions of which vary with the proportions of ester and amide entering the reaction (333).

Scheibler (301) in his controversial preparation of carbon monoxide diethyl acetal, $C(OC_2H_5)_2$, states that sodium amide reacts with ethyl formate in ethereal solution to give ammonia and sodium oxy-ethoxymethylene, $C(OC_2H_5)(ONa)$, in accordance with the equation

$$HCOOC_2H_5 + NaNH_2 = NH_3 + C(OC_2H_5)(ONa) \qquad (110)$$

Nitrogen-containing by-products are formed at the same time. Titherley (333) previously reported his inability to obtain a sodium salt of ethyl formate, while Wood and the senior author (38) did not succeed in preparing it in liquid ammonia.

Phenyl benzoate is saponified in the approximate manner of equation 107 to phenol and the sodium salt of dibenzamide, $(C_6H_5CO)_2NNa$. The latter may be formed by the action of the expected product, sodium benzamide, $C_6H_5CONHNa$, upon a molecule of the unchanged ester (333).

$$C_6H_5CONHNa + C_6H_5COOC_6H_5 = (C_6H_5CO)_2NNa + C_6H_5OH \qquad (111)$$
$$\text{(or } C_6H_5ONa)$$
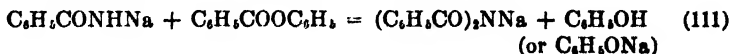
Diethyl oxalate reacts very vigorously with sodium amide in the absence of a diluent (335). The reaction is more regular in the presence of an excess of benzene, but in spite of this the sodium salts of oxamic acid and of oxamide are formed only in poor yield.

Benzimino ethyl ether, $C_6H_5C(=NH)OC_2H_5$, an O-ester of a mixed aquoammonobenzoic acid, benzamide, reacts with sodium

amide in benzene to form sodium ethylate, benzonitrile, and ammonia (335).

$$C_6H_5C(=NH)OC_2H_5 + NaNH_2 = C_6H_5CN + C_2H_5ONa + NH_3 \quad (112)$$

A molecule of ethyl alcohol is removed, converting the ester to benzonitrile, an anammonide of ammonobenzoic acid, C_6H_5C $(=NH)NH_2$. As we have seen, benzonitrile may itself react with sodium amide (cf. equation 90).

Ramart and Haller (284), in extending the earlier work of Titherley, have likewise come to the conclusion that the action of sodium amide on esters varies with the nature of the ester and with the experimental conditions. Phenyl formate is decomposed by sodium amide into sodium phenolate, carbon monoxide, and ammonia, a more deep-seated decomposition than Titherley observed with the alkyl esters of formic acid. Phenyl acetate is converted to sodium phenolate and acetamide, in the manner to be expected from equation 107. Benzyl isobutyrate and sodium amide react, in the absence of solvent, with the evolution of ammonia, but the unchanged ester alone is recovered after hydrolysis of the reaction mixture. This would indicate the formation of a salt. If the reaction is carried out at higher temperatures, under xylene, the ester is to some extent saponified.

The benzyl ester of phenylacetic acid reacts with sodium amide suspended in warm ether or benzene with the slow evolution of ammonia. The addition of benzyl chloride, after completion of the reaction, gives sodium chloride, phenylacetamide and its N-benzyl derivative (cf. equation 107), the latter obviously formed by the action of benzyl chloride on sodium phenylacetamide.

If benzyl phenylacetate and sodium amide react at 0°C. in the absence of solvent, a sodium salt of the ester is formed, $C_6H_5CHNaCOOCH_2C_6H_5$. The sodium salt may well have the enolic structure, $C_6H_5CH=C(ONa)OCH_2C_6H_5$.

Ramart (282a) and Ramart and Amagat (283b) have alkylated esters of diphenyl- and phenyl-p-tolylacetic acids in accordance with the illustrative equation

$$p\text{-CH}_3\text{—C}_6\text{H}_4 \diagdown \underset{\text{C}_6\text{H}_5 \diagup}{}\text{CHCOOCH}_2\text{C}_6\text{H}_5 \xrightarrow{\text{NaNH}_2} p\text{-CH}_3\text{—C}_6\text{H}_4 \diagdown \underset{\text{C}_6\text{H}_5 \diagup}{}\text{C(Na)COOCH}_2\text{C}_6\text{H}_5$$

$$\xrightarrow{\text{CH}_3\text{I}} \underset{\text{C}_6\text{H}_5}{} p\text{-CH}_3\text{—C}_6\text{H}_4 \atop \cdot\text{C(CH}_3)\text{COOCH}_2\text{C}_6\text{H}_5 \qquad (112a)$$
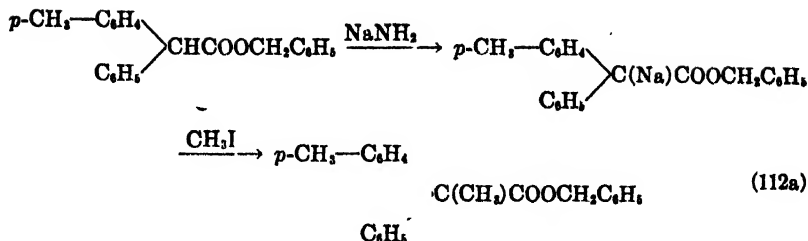
The sodium salt pictured above is undoubtedly derived—at least in large measure—from the enol form of the ester.

Staudinger and Meyer (319a) state that methyl diphenylacetate reacts with potassium amide in liquid ammonia to form an addition compound, from which ammonia can be removed by heating in a vacuum at 100–110°C., presumably leaving the salt of the enol, $(C_6H_5)_2C\text{=}C(ONa)OCH_3$. This is converted to the methyl ester of methyldiphenylacetic acid by the action of methyl iodide.

Titherley (332) reports that potassium ethyl sulfate reacts with sodium amide at 180°C. in "petrol" to form ammonia, ethylene, and ethylamine, the latter in about 10 per cent of the theoretical yield. Picon (279) has obtained similar results.

Chichibabin and Rjasanjew (85a) treated 2-aminopyridine with sodium amide and the resulting sodium salt with isoamyl nitrite, obtaining a comparatively stable isodiazotate of 2-aminopyridine, $C_5H_4N\cdot N\text{=}NONa$. It is known that aniline is converted by a solution of sodium ethylate and isoamyl nitrite into the sodium salt of isodiazobenzene, $C_6H_5\text{—}N\text{=}N\text{—}ONa$ (11, 92).

Blair (42) finds that ethyl allophanate, $NH_2CONHCOOC_2H_5$, reacts with a solution of potassium amide in liquid ammonia to form a monopotassium salt, as would be predicted from the fact that we are dealing with an acid ester of a mixed aquoammonocarbonic acid. Potassium replaces one of the three hydrogens attached to nitrogen. Heated in the absence of liquid ammonia to 215°C., this salt is split into urethan and potassium cyanate, an ethyl ester and a potassium salt of two different mixed aquoammonocarbonic acids. Using potassium amide in excess of three equivalents, Blair was able to saponify ethyl allophanate in

liquid ammonia at ordinary temperatures.   The reaction appears
to be complex.

Ethylcarbamate, or urethan, $NH_2COOC_2H_5$, is readily saponi-
fied by potassium amide in liquid ammonia at room temperatures
(42), in accordance with the equation

$$NH_2COOC_2H_4 + KNH_2 = KNCO + C_2H_4OH \text{ (or } C_2H_4OK) + NH_3 \quad (113)$$
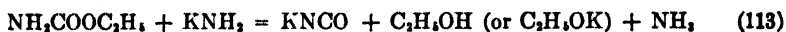
Since cyanamide, NH_2CN, is an ammonocarbonic acid (127),
it follows that the dialkylcyanamides, R_2NCN, are esters.   In
conformity with this view, Griswold (158) reports that a dialkyl
amine (an ammono alcohol) and dipotassium cyanamide result
from the action of a liquid ammonia solution of two or more
equivalents of potassium amide on these esters at temperatures
above 35°C.   Diethylcyanamide is thus decomposed in the man-
ner of the equation

$$(C_2H_6)_2NCN + 2KNH_2 = (C_2H_6)_2NH + K_2NCN + NH_3 \quad (114)$$
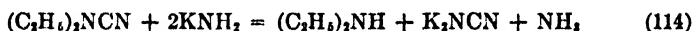
At the temperature of an ice-salt freezing mixture ($-6°C$. or
below) equimolecular proportions of potassium amide and a
dialkylcyanamide unite to form crystalline addition compounds
which appear to be derivatives of guanidine.

$$(C_2H_6)_2NCN + KNH_2 = (C_2H_6)_2NC(=NH)NHK \quad (115)$$
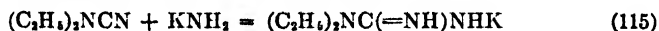
B. Esters undergoing the Claisen condensation

Titherley (333) was the first to observe that sodium amide
reacts with ethyl acetate dissolved in benzene to form the sodium
salt of ethyl acetoacetate and ammonia.   The yield of product
is not as good as in the reaction between ethyl acetate and metallic
sodium.   Freund and Speyer (138) almost simultaneously con-
densed ethyl acetate with sodium amide in the absence of an inert
liquid and obtained sodium acetoacetic ester, likewise in poor
yield.   A few years later, Claisen and Feyerabend (98) extended
the earlier work of Titherley and of Freund and Speyer, and dis-
covered that sodium amide can be used to advantage in the con-
densation of ketones with esters to form 1,3-diketones, in that
the reactions often run more smoothly and rapidly and give better
yields of product.   As an illustration, sodium amide was slowly

introduced into a mixture of ethyl acetate and acetone, cooled in a freezing mixture. After a few hours standing at 0°C. and about twelve hours standing at room temperatures, ice water was slowly added to hydrolyze the reaction products, and the acetylacetone contained in the aqueous layer was isolated as the copper salt, after previously acidifying the solution with acetic acid. From 34 grams of sodium amide, 120 cc. of ethyl acetate, and 32 cc. of acetone, there was obtained 20 grams of acetylacetone, while only 16 to 17 grams could be prepared by the older method in which sodium was used. It is of significance that these directions have been transferred to Gattermann-Wieland, *Die Praxis des organischen Chemikers* (149).

Benzoylacetone was obtained in 77 per cent of the theoretical yield by condensing ethyl acetate and acetophenone with sodium amide in ether (98). Acetophenone, ethyl benzoate, and sodium amide in ether gave dibenzoylmethane in good yield. Oxymethylene ketones of the type, $CH_3COCH{=}CHOH$, may be prepared by the condensation of formic acid esters with ketones in the presence of sodium amide.

$$HCOOC_2H_5 + CH_3COCH_3 \xrightarrow{\text{NaNH}_2} C_2H_5ONa + NH_3 + CH_3COCH_2CHO \qquad (116)$$
$$\updownarrow$$
$$CH_3COCH{=}CHOH$$
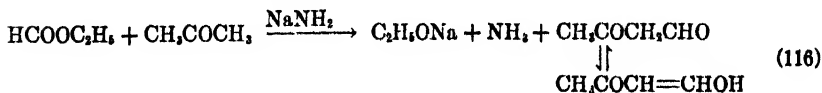
An internal Claisen condensation, or Dieckmann reaction, may be occasioned by sodium amide in long chain esters of suitable constitution. Bouveault and Locquin (74) have carried out a number of syntheses of this type, of which the following is an example.

$$
\begin{array}{ccc}
CH_2CH_2COOC_2H_5 & & CH_2CH{-}COOC_2H_5 \\
& \dfrac{+\ \text{NaNH}_2}{-\ C_2H_5OH} & \diagdown\!\!\diagup CO \qquad (116a) \\
CH_2CH(CH_3)COOC_2H_5 & & CH_2CH{-}CH_3 \\
\text{Diethyl } \alpha\text{-methyladipate} & & \text{Ethyl } \alpha\text{-methylcyclo-} \\
& & \text{pentanone-}\alpha'\text{-carboxylate}
\end{array}
$$
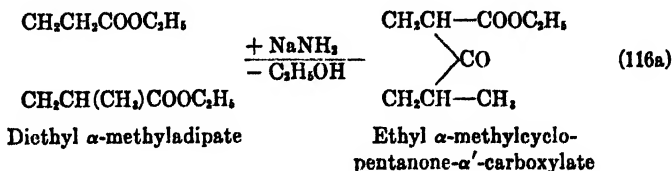
Bauer (18a) in a like manner prepared α-benzoylcyclopentanone and α-benzoylcyclohexanone by the action of sodium amide on esters of δ-benzoylvaleric and ϵ-benzoylcaproic acids, respec-

tively. The latter may also be made by condensing ethyl benzoate with cyclohexanone in the presence of sodium amide (20). (See also reference 361.)

Claisen and Schulze (95) obtained 32 per cent of the calculated amount of isonitrosoacetophenone by the action of sodium amide on a mixture of amyl nitrite and acetophenone, while the same substance was prepared in 50 per cent yield by using sodium ethylate in place of the sodium amide. There is accordingly no advantage in the use of the latter in this synthesis.

A number of years later, Scheibler and his coworkers, in a series of investigations of the action of finely divided alkali metals on the esters of the lower fatty acids, came to the conclusion that the first product of the action of potassium upon ethyl acetate in absolute ether has the structure, $CH_2\!=\!C(OC_2H_5)(OK)$, this representing the sodium salt of the enolic form of the ester (306, 307, 303).   •

$$CH_3COOC_2H_5 + K \rightarrow CH_2\!=\!C(OC_2H_5)(OK) + \tfrac{1}{2}H_2 \tag{117}$$
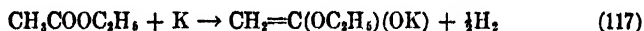
Since sodium amide may replace metallic sodium in the acetoacetic ester condensation, it naturally became of interest to examine further the reaction between this ammono base and ethyl acetate. This was done by Scheibler and Ziegner (307) who conclude that the reaction follows the course,

$$CH_3COOC_2H_5 + NaNH_2 = CH_3\!-\!\overset{\displaystyle \overset{OC_2H_5}{\diagup}}{\underset{\displaystyle \underset{NH_2}{\diagdown}}{C}}\!-\!ONa \xrightarrow{-NH_3} CH_2\!=\!C(OC_2H_5)(ONa) \tag{118}$$
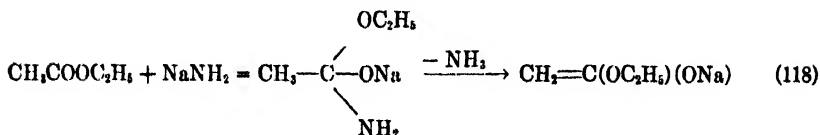
The conversion of the sodium enolate of ethyl acetate into ethyl acetoacetate may be expressed by the equation

$$CH_2\!=\!C\!\!\underset{\diagdown ONa}{\overset{\diagup OC_2H_5}{}} \tag{119}$$

$$\underset{CH_3CO\!-\!OC_2H_5}{} \rightarrow CH_3COCH_2C(OC_2H_5)_2(ONa) \xrightarrow[-NaOC_2H_5]{CH_3COOH} CH_3COCH_2COOC_2H_5$$
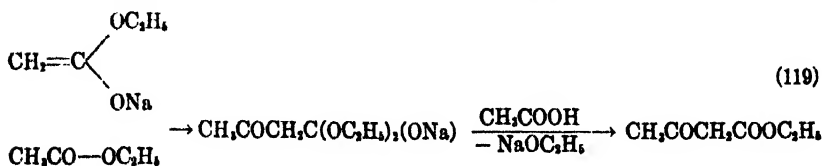
K. Meyer holds a similar view concerning the mechanism of this condensation (263) and speculations concerning the possible existence of the enolic salt of equation 117 are found in Gattermann-Wieland, *Die Praxis des organischen Chemikers* (149a).

When the product of the action of sodium amide upon an excess of ethyl acetate (to which ether was later added) is freed by vacuum distillation from the excess of ester and ether, there is left a colorless solid consisting of the addition product, $CH_3COCH_2C(OC_2H_5)_2(ONa)$. If this is added very slowly to ice water, some sodium acetate and ketene diethylacetal are formed in the sense of the equation (309),

$$CH_3COCH_2C \begin{matrix} OC_2H_5 \\ | \\ ONa \\ | \\ OC_2H_5 \end{matrix} = CH_3COONa + CH_2{=}C(OC_2H_5)_2 \qquad (119a)$$

Ketene diethylacetal
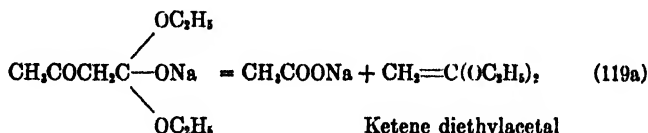
The yield is not over 16 per cent of the theoretical amount calculated on the basis of the sodium amide.

According to Scheibler, Marhenkel, and Nikolić (305), ketene diethylacetal is decomposed by eight hours refluxing with sodium amide under diethyl ether into ethinyl ethyl ether, according to the scheme

$$CH_2{=}C(OC_2H_5)_2 \xrightarrow[- C_2H_5ONa]{+ NaNH_2} CH_2{=}C(OC_2H_5)NH_2 \xrightarrow{- NH_3} CH{\equiv}COC_2H_5 \qquad (120)$$
$$+ NaNH_2 \downarrow$$
$$NaC{\equiv}COC_2H_5$$
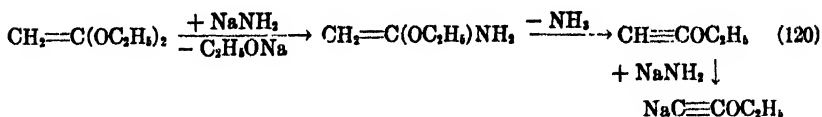
Phenylketene diethylacetal, $C_6H_5CH{=}C(OC_2H_5)_2$, was submitted to a similar series of operations to give phenylethinyl ethyl ether, $C_6H_5C{\equiv}COC_2H_5$. It should be mentioned that both of these acetylenic ethers were qualitatively recognized by their reactions but were not isolated.

Scheibler and Ziegner (308) have briefly investigated the action of sodium amide upon a mixture of ethyl acetate and ethyl benzoate.

Finally, it is only fair to say that the views of Scheibler and his coworkers concerning the mechanism of the acetoacetic ester

synthesis have been attacked by Adickes (1) and by M. C. Franklin and Short (137). The latter authors have not been able to duplicate in all particulars the work of Scheibler and his coworkers on the sodium amide–ethyl acetate reaction. They have observed the formation of sodium acetate and sodium acetamide, in qualitative agreement with the earlier work of Titherley (333).

XIV. ORGANIC DERIVATIVES OF HYDROXYLAMINE, HYDRAZINE, DIIMIDE, AND TRIAZENE

Oximes, such as acetone oxime, are readily converted by sodium amide in warm benzene to salts of the type, $(CH_3)_2C=NONa$ (329). Phenylhydrazine reacts with sodium amide in benzene at 40°C. to form a pale yellow monosodium salt, in which the alkali metal is supposed to be attached to the nitrogen nearest the phenyl group (329).

Titherley (330) makes the unsupported statement that sodium hydrazobenzene has been prepared in a manner similar to sodium phenylhydrazine. Schurman and Fernelius (314) state that hydrazobenzene reacts with potassium amide in liquid ammonia to form a very soluble strongly colored reddish-brown salt. As the color is discharged by ammonium salts, which act as acids in liquid ammonia (125, 133, 135, 33), hydrazobenzene is suitable for use as an indicator of the Ostwald type.

White and Knight (343) observed that potassium amide reacts with phenylhydroxylamine in liquid ammonia at −33°C. to form a sparingly soluble, red precipitate, which they consider to be identical with the red dipotassium phenylhydroxylamine formed by the action of potassium metal on nitrobenzene in liquid ammonia.

$$C_6H_5NO_2 + 4K + NH_3 = KOH + KNH_2 + C_6H_5N(K)OK \qquad (121)$$
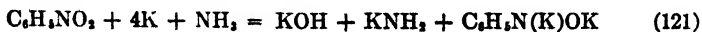
Sachs (299) claims to have obtained hydrazobenzene as one of the products of the reaction between fused sodium amide and azobenzene.

Meunier and Desparmet (260) state that diazoaminobenzene

reacts with sodium amide in ether to form a sodium salt, in the manner of the equation

$$C_6H_5NHN{=}NC_6H_5 + NaNH_2 = C_6H_5NNaN{=}NC_6H_5 + NH_3 \quad (122)$$

Fernelius (118) has found that diazoaminobenzene reacts with the amides of calcium and barium in liquid ammonia to form salts of the general formula,

$$\left[\begin{array}{c} C_6H_5N{=}N \\ \diagdown \\ \quad N{-} \\ \diagup \\ C_6H_5 \end{array}\right]_2 Ba{\cdot}xNH_3$$
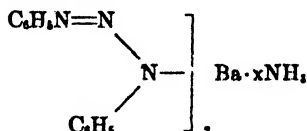
in agreement with Franklin's theory (124) that the parent compound is a diphenyl ester of an ammononitrous acid, $HN{=}N{-}NH_2$. (The central nitrogen is the nitrous acid nitrogen.) Potassium and sodium amide in liquid ammonia convert diazoaminobenzene to extremely soluble salts that can not be isolated in crystalline form.

XV. NITRO COMPOUNDS

In an attempt to reverse the ordinary method of formation of diazonium salts, in which a salt of aniline is treated with sodium nitrite and an acid, Bamberger and Wetter (12; cf. Sachs reference 298, and Titherley, reference 328) treated nitrobenzene with sodium amide suspended in cold petroleum ether, to which β-naphthol had been added. From the products of the hydrolysis of the reaction mixture, there was isolated a small quantity of phenylazo-β-naphthol, a compound that is likewise formed by the coupling of potassium benzene normal diazotate with an alkaline solution of β-naphthol in water,

$$\overset{1}{C_6H_5{-}N}{=}N{-}OK + C_{10}H_7OH = \overset{2}{C_6H_5{-}N}{=}N{-}C_{10}H_6OH + KOH \quad (123)$$
$$\text{Phenylazo-}\beta\text{-naphthol}$$
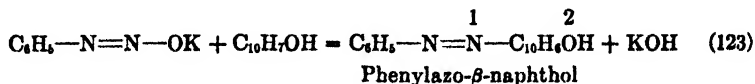
Williams (347), working in the laboratories of Stanford University, undertook the examination of this reaction in liquid ammonia at −33°C., and found that nitrobenzene, added slowly

to a solution of an excess of potassium amide and β-naphthol gives a fair yield of phenylazo-β-naphthol (see equation 123).

The senior author (34) found that nitrobenzene reacts vigorously with a liquid ammonia solution of potassium amide at −33°C. or at room temperature, with the evolution of nitrogen. The product of the reaction must therefore be rather unstable in ammonia, a not unexpected fact since benzenediazonium nitrate reacts with this solvent to give an indefinite mixture of a somewhat similar nature. p-Nitroaniline, o-nitroaniline and 1-nitronaphthalene also react with a liquid ammonia solution of potassium amide at room temperatures to give mixtures from which no definite compounds have been isolated. p-Nitrotoluene, reacting with β-naphthol and an excess of potassium amide in ammonia at room temperatures, is converted in good yield to a red colored dye.

Angeli (8a) has mentioned this reaction of Bamberger and Wetter's as an indication of the correctness of his proposed structure for normal potassium benzene diazotate, C_6H_5—N(=NK)O (8, 8a).

Fernelius and Watt (120) report that diphenylnitrosoamine, a diphenyl ester of a mixed aquoammononitrous acid, reacts with potassium amide to give diphenylamine, nitrogen, and potassium hydroxide

$$(C_6H_5)_2N\text{---}NO + 2KNH_2 = NH_3 + (C_6H_5)_2NK + (O=N\text{---}NHK) \quad (124)$$
$$(O=N\text{---}NHK) = KOH + N_2$$
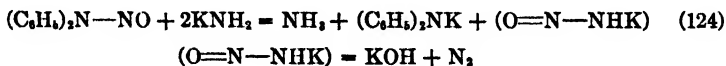
the two latter substances possibly resulting from the decomposition of a primarily formed potassium salt of a mixed aquoammononitrous acid, O=N—NHK. Similar reactions were observed with the amides of lithium, sodium, and calcium.

XVI. FIVE-MEMBERED HETEROCYCLIC NITROGEN RING SYSTEMS

The N-hydrogen atoms of pyrrole, indole, and carbazole, as is well known, are slightly acidic in character, since they may be replaced by metals. The reason why these substances do not show the basic properties usually associated with trivalent nitrogen is probably due to the inclusion of the unshared electron pair

of the nitrogen atom in a group of six electrons inside of the heterocyclic ring (10, 224, 156). Nitrogen thus has no unshared electron pairs external to the nucleus and this will hinder its coördination with the hydrogen-ion. It is thought that the aromatic properties of benzene are due to this same stable grouping of six electrons within the molecule.

Although not the first to prepare alkali salts of pyrrole, indole, and carbazole, Franklin (131) was the first to observe that these heterocyclic nitrogen compounds react with the metallic amides in liquid ammonia. Sodium and silver amides convert pyrrole, indole, and carbazole to their sodium and silver salts, which may readily be obtained in crystalline form by cooling their liquid ammonia solutions. The formation of sodium pyrrole may serve as an illustration.

$$C_4H_4NH + NaNH_2 + (x - 1)NH_3 = C_4H_4NNa \cdot xNH_3 \qquad (125)$$

Calcium carbazole is readily prepared by treating carbazole with calcium amide in liquid ammonia. Potassium amide reacts with pyrrole, indole, and carbazole, but with the exception of potassium carbazole, none of the salts were isolated and analyzed.

Strain (322) refers to the work of Wenzel (342), who prepared the potassium, sodium, calcium, and silver salts of imidazole
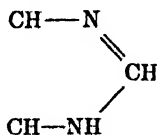
by the action on this substance of the appropriate metallic amide in liquid ammonia. Bergstrom and Wood (38) made the monosodium and monopotassium salts of benzimidazole,
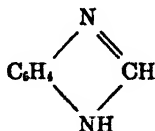
and Strain obtained the monosodium, silver, and cuprous salts of 1,2,4-triazole

$$CH=N$$
$$\diagdown$$
$$NH$$
$$\diagup$$
$$N=CH$$
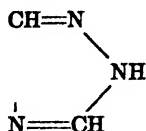
and the monopotassium, sodium, cuprous, silver, and lithium salts of triphenylglyoxaline (lophine),

$$C_6H_5C-N$$
$$\diagdown\diagdown$$
$$CC_6H_5$$
$$\diagup$$
$$C_6H_5\dot{C}-NH$$
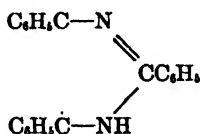
by the general methods outlined above (322).

As may be seen from the formulas above, these substances may be regarded as acid esters of ammonoformic acid, $H-C(=NH)-NH_2$. Tetrazole is also an ester of a hydrazide of formic acid.

XVII. SIX-MEMBERED HETEROCYCLIC NITROGEN RING SYSTEMS

A. Pyridine and its derivatives

Chichibabin and his coworkers (310, 81, 87, 150) prepared 2- or α-aminopyridine, $C_5H_4N-NH_2$, in yields that are reported as high as 70 per cent, by the action of sodium amide upon pyridine in boiling xylene, toluene, or benzene, the reaction following the equation

$$C_5H_5N + NaNH_2 = H_2 + C_5H_4N-NHNa \qquad (126)$$

Water converts the sodium salt above into 2-aminopyridine, which may be extracted from the aqueous solution with benzene. The preparation of 2-aminopyridine has been the subject of a number of patents (81, 310).

Several years later, Wibaut and Dingemanse (346) again investigated the action of sodium amide on pyridine in toluene, and obtained results differing in a few details from those of Chichibabin. Distillation in a vacuum of the ether extract of the hydrolysate of the sodium amide–pyridine reaction mixture gave 2-aminopyridine in 46 to 55 per cent yield, along with higher

boiling fractions which contained smaller amounts of 4,4'-dipyridyl, 2,2'-dipyridylamine and unidentified products. Chichibabin likewise obtained higher boiling fractions, but he was unable to identify any constituent with certainty.

Wibaut and Dingemanse (346) made the interesting observation that the yield of 2-aminopyridine depends to a large extent upon the condition of the sodium amide used in the synthesis. Strangely enough, it was found that the purest sodium amide, prepared in accordance with the method of Titherley (327), failed to react appreciably with pyridine during eight hours heating at 120–125°C. in toluene, while good yields of 2-aminopyridine were obtained when sodium amide of less purity was used (i.e., material of commercial origin or material that had been standing in laboratory bottles for some time). It would appear that impurities in the sodium amide have catalytically influenced the course of the reaction.

If the relative proportion of sodium amide is increased above that used in the preparation of 2-aminopyridine, it is possible under suitable conditions to introduce another amino group into the pyridine nucleus and obtain 2,6-diaminopyridine in yields of about 50 per cent (87).

$$\text{(pyridine ring)}\!-\!NH_2 + NaNH_2 = 2H_2 + H_2N\!-\!\text{(pyridine ring)}\!-\!NH_2 \quad \text{(as the sodium salt)} \quad (127)$$
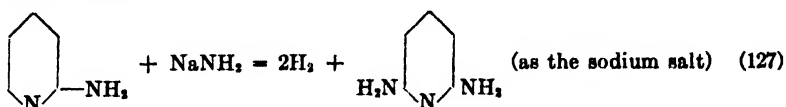
The mechanism of these syntheses has been discussed by Ziegler and Zeiser (356), who suggest that the sodium amide first adds to the $-CH\!=\!N-$ bond of pyridine to give

$$\text{(ring)}\ CHNH_2 \quad \text{or} \quad \text{(ring)}\ CHNHNa \quad (127a)$$

$$\underset{Na}{|}\qquad\qquad \underset{H}{|}$$
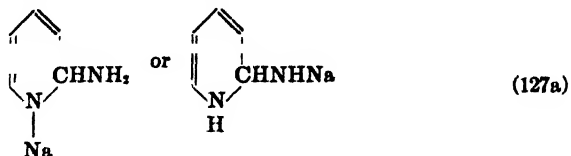
this passing by loss of sodium hydride into 2-aminopyridine. The sodium hydride cannot be isolated as such, since it converts 2-aminopyridine into a sodium salt and hydrogen.

$$C_5H_4N\!-\!NH_2 + NaH = (C_5H_4N\!-\!NH)Na + H_2 \quad (128)$$
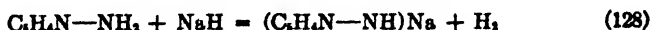
One could equally well assume that the direct loss of a molecule of hydrogen from 127a gives sodium 2-aminopyridine.

Although this mechanism received no direct experimental support, it appeared reasonable because the addition products formed between pyridine and the lithium alkyls or aryls lose lithium hydride on heating and pass into 2-alkyl- or 2-arylpyridines.

$$
\begin{array}{ccc}
\text{CH} + \text{RLi} & \text{CHR} & \xrightarrow{-\text{LiH}} \text{CR} \qquad (129) \\
\end{array}
$$
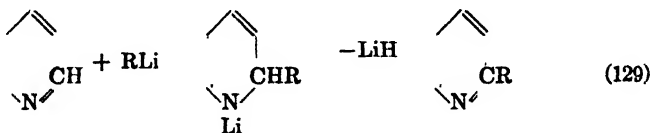
In a series of unpublished investigations, one of us (34) has shown that pyridine reacts slowly with a liquid ammonia solution of a large excess of potassium amide at room temperatures to yield 2-aminopyridine in amounts not greater than 30 per cent of the theoretical. A large excess of pyridine, on the other hand, results in the formation, in poor yield, of a soluble blue colored monopotassium salt of a partly reduced 4,4'-dipyridyl. (Compare the blue color produced when 4,4'-dipyridyl is treated with zinc dust and acetic acid, as in the qualitative test for this substance (cf. reference 115a). Very little or no 2-aminopyridine is formed. The other product of the reactions is an amorphous, apparently polymerized substance that chars without melting.

Heated to 100–130°C. with an excess of a liquid ammonia solution of potassium amide, pyridine is partly converted to the potassium salts of 2-aminopyridine and 2,6-diaminopyridine, with the evolution of some hydrogen. The potassium salt of 2-aminopyridine is readily soluble in liquid ammonia, while the dipotassium salt of diaminopyridine is practically insoluble. Bergstrom and McAllister (35) have pointed out the formal structural relationship of the —CH=N— group of pyridine to the —CH=O group of the aquo aldehydes. The formation of 2-aminopyridine is therefore the nitridation of an aldehyde of the ammonia system to the corresponding carbazylic acid, which contains the group

$$
\begin{array}{c}
\text{N---} \\
\diagup\!\!\diagup \\
\text{---C---NH}_2
\end{array}
$$
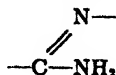
It is well known from the work of Chichibabin (86) that 2-aminopyridine is readily converted to a sodium salt by reaction with sodium amide under benzene. This salt, when heated with alkyl halides or with dimethyl sulfate, is changed to 2-N-alkylated aminopyridines.

2-Methylpyridine (α-picoline) reacts with sodium and potassium amide in liquid ammonia to form salts of an enamic, or ammono enolic, modification (31), in the manner of the equation

$$\text{(130)}$$
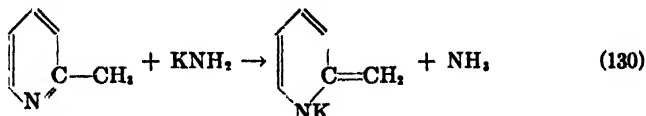
Working with sodium amide in a boiling hydrocarbon solvent, Seide (315b) and Chichibabin (86, 81, 310) have found that 2-methylpyridine is converted in fair yield to 2-methyl-6-aminopyridine.

$$\text{(131)}$$
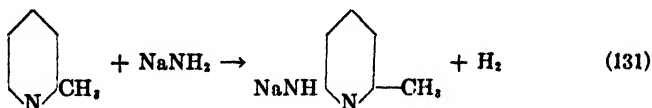
3-Methylpyridine (316), 4-methylpyridine (315a), 2-methyl-5-ethylpyridine (aldehyde collidine) (90), and nicotine (83, 84), when treated with sodium amide under similar conditions, are converted respectively to 2-amino-3-methylpyridine, 2-amino-4-methylpyridine, 2-methyl-5-ethyl-6-aminopyridine and to a mixture of α- and α'-aminonicotines.

Symmetrical collidine (2,4,6-trimethylpyridine) is changed by an excess of potassium amide in liquid ammonia solution at room temperature to the potassium salt of an ammono enol (enam), but barium and sodium amide, having a low solubility in ammonia, do not react to completion (32).

From the above reactions it would appear that the nitrogen atom has in some way activated the hydrogen atoms in the α and α' positions alone, so that one or both may be replaced by amino groups. Whether this activation can be attributed other than in a purely formal manner to the inclusion of the ammono alde-

hyde group, —CH=N—, in the pyridine ring, is a matter that must await further investigation.

Chichibabin believed that he found a little 4-aminopyridine among the products of the action of sodium amide on pyridine, but this was not confirmed by Wibaut and Dingemanse. Nevertheless, Chichibabin (82) reports that sodium amide and 2,6-dimethylpyridine slowly react to form a small amount of the 4-amino derivative.

B. Quinoline, isoquinoline, and their derivatives

Chichibabin and Zatzepina (91) prepared 2-aminoquinoline in rather poor yield (25 per cent) by heating quinoline and sodium amide in the presence of a boiling hydrocarbon. 2,3-Diquinoline is formed at the same time, and this readily loses two atoms of hydrogen by oxidation and passes into 2,3-diquinolyl. The formation of 2,3-diquinoline from quinoline may be regarded as an example of the aldol condensation, if one accepts the thesis that quinoline has some of the properties of an aldehyde of the ammonia system (35). The condensation may be represented by the equation

$$C_6H_4\left\langle\begin{array}{c}CH = CH\\|\quad\quad|\\N = CH\end{array}\right. + \left|\begin{array}{c}CH=CH\\\\CH=N\end{array}\right\rangle C_6H_4 = C_6H_4\left\langle\begin{array}{cc}CH=C\\|\quad\quad|\\N=CH\end{array}\right.\left.\begin{array}{c}CH=CH\\|\\CH-NH\end{array}\right\rangle C_6H_4$$

2,3-Diquinoline

$$\xrightarrow{(O)} C_6H_4\left\langle\begin{array}{cc}CH=C\\|\quad\quad|\\N=CH\end{array}\right.\left.\begin{array}{c}CH=CH\\|\\C=N\end{array}\right\rangle C_6H_4 \qquad (132)$$

2,3-Diquinolyl
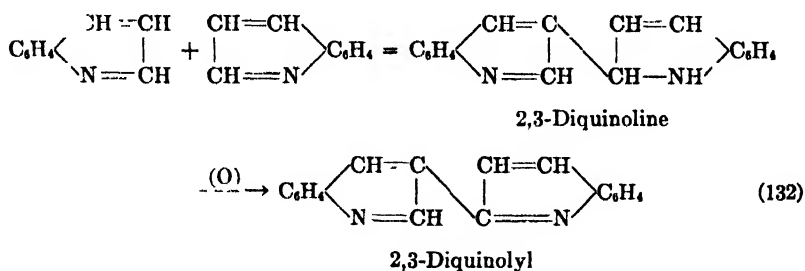
In liquid ammonia solution at room temperatures, both sodium and potassium amide convert quinoline into low-melting resinous compounds of an indefinite nature (34). 2-Aminoquinoline is, however, formed in good yield, together with the calculated amount of hydrogen, by the action of barium amide upon quinoline in liquid ammonia, possibly because the reaction is slower as a result of the low solubility of the barium amide (34). One may recall in this connection that strong aqueous or alcoholic

potassium hydroxide converts acetaldehyde into indefinite "aldehyde resins," while weaker alkalis, such as potassium carbonate, favor the formation of a definite compound, which in this case is an aldol (265, 274).

1-Aminoisoquinoline may be prepared in 38 per cent yield by the action of sodium amide upon isoquinoline in the presence of hot indifferent solvents (85). A solution of potassium amide in liquid ammonia at room temperatures reacts with isoquinoline to give 1-aminoisoquinoline in 75 per cent yield (34), together with approximately the amount of hydrogen that corresponds to the equation

$$C_6H_4 \diagup \begin{matrix} CH=\!=CH \\ | \\ CH=\!-N \end{matrix} + KNH_2 = C_6H_4 \diagup \begin{matrix} CH=\ CH \\ | \\ C=\!=\!=N \\ | \\ NHK \end{matrix} + H_2 \qquad (133)$$
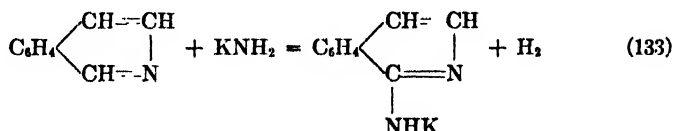
Quinaldine, 2-methylquinoline, reacts readily with potassium or sodium amide in liquid ammonia, either at $-33°C$. or at room temperatures, to form soluble red colored salts of an ammono enolic, or enamic, modification (29), in the manner represented by the equation

$$C_6H_4 \diagup \begin{matrix} CH=\!=CH \\ | \\ N=\!=C-CH_3 \end{matrix} + KNH_2 = C_6H_4 \diagup \begin{matrix} CH=\!=CH \\ | \\ NK-C=\!=CH_2 \end{matrix} + NH_3 \quad (134)$$
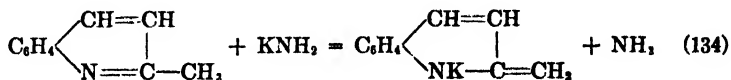
Regarding quinaldine as a cyclic ammono ketone (acetal) because of the

$$\begin{matrix} CH_2 \\ \diagdown \\ \diagup \\ =\!-CH \end{matrix} C\text{-}\!=\!N-$$
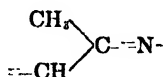
group, it is perfectly logical to assign to the reaction product of equation 134 the structure of an ammono enol, which contains the group,

$$\begin{matrix} H_2C \\ \diagdown \\ \diagup \\ =\!=CH \end{matrix} C-NK-$$
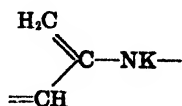
These salts may readily be alkylated in liquid ammonia or in absolute ether to form homologues of quinaldine, in accordance with the type equation

$$C_6H_4\begin{array}{c}CH=CH\\|\\NK-C=CH_2\end{array} + C_2H_5Br = C_6H_4\begin{array}{c}CH=CH\\|\\N=C-CH_2C_2H_5\end{array} + KBr \quad (135)$$
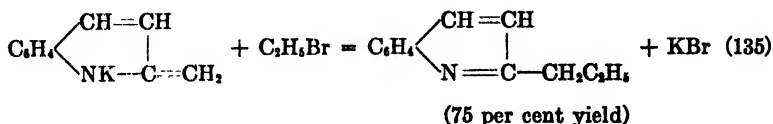
(75 per cent yield)

The reaction proceeds less satisfactorily with n-butyl and n-amyl bromide, the yield of n-amylquinoline with the former amounting to about 25 per cent. 2-Ethyl- and 2-n-butyl quinolines have been prepared in fair yields by this method.

All quinoline derivatives with a —CH_2— group in the 2-position (as, for example, 2-ethyl- and 2-ω-phenylethylquinoline) react with potassium amide to form homologues of potassium quinaldine, in the manner of equation 134. These salts may be alkylated by treatment with alkyl halides in the *absence* of liquid ammonia, as in the typical preparation of 2-*sec*-butylquinoline from 2-ethylquinoline (32a).

$$C_6H_4\begin{array}{c}CH=CH\\|\\N=C-CH_2CH_3\end{array} \xrightarrow{KNH_2} C_6H_4\begin{array}{c}CH=CH\\|\\NK-C=CHCH_3\end{array}$$

$$\xrightarrow{C_2H_5Br} C_6H_4\begin{array}{c}CH=CH\\|\\N=C-CH\begin{array}{c}CH_2CH_3\\CH_3\end{array}\end{array} \quad (136)$$
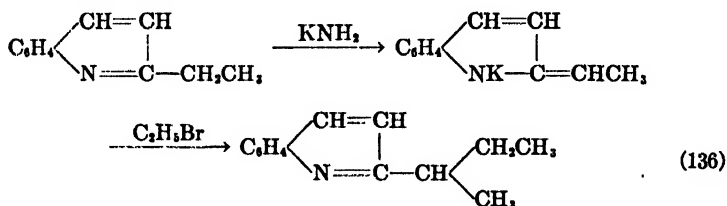
4-Methylquinoline (lepidine) reacts with potassium, sodium, and barium amides in liquid ammonia to form salts of the probable type constitution,

$$C_6H_4\begin{array}{c}CH_3\\||\\C-CH\\||\\NK-CH\end{array}$$
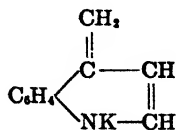
These salts can be alkylated by treatment with the lower alkyl halides in ethereal solution. 4-Ethyl- and 4-n-propyl-quinolines were thus prepared (32a).

Ziegler and Zeiser have alkylated quinoline through the lithium salt of the enamic modification, prepared by the action of lithium alkyls or aryls on quinaldine in ether (356).

C. *Pyrazine and 2,5-dimethylpyrazine*

Bergstrom and Ogg (37) found that pyrazine
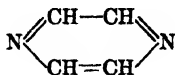
is attacked by a liquid ammonia solution of potassium amide to form an opaque dirty green solution from which no definite products were isolated.

According to Chichibabin and Shchukina (89), 2,5-dimethylpyrazine slowly reacts with sodium amide in xylene to give 2,5-dimethyl-3-aminopyrazine in poor yield. In the absence of solvent, some dimethylpiperazine is formed by reduction of the dimethylpyrazine and there is also obtained a tetramethyldipyrazyl and a trimethyldipyrazylmethane, of the formulas.

(137)

Tetramethyldipyrazyl   Trimethyldipyrazylmethane
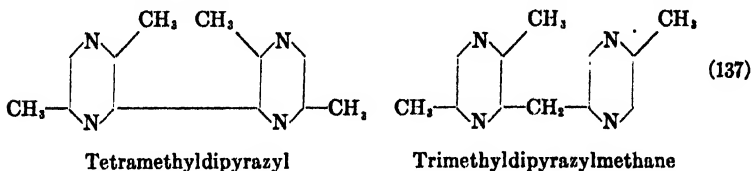
D. *Quinoxaline and its derivatives*

Quinoxaline
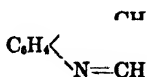
is readily formed by the action of glyoxal, CHO-CHO, on *o*-phenylenediamine, a reaction which may be interpreted as the ammonolysis of an aquo dialdehyde by a substituted ammonia to give the *o*-phenylene diacetal of a glyoxal of the ammonia system. The resemblance of quinoxaline to glyoxal is often rather striking. Confining ourselves only to reactions in which

the alkali amides have a part, we find that potassium amide, in
ammonia solution, converts quinoxaline into a mixture which
appears to contain the dipotassium salt of fluorubin (36).

$$C_6H_4\left\langle\begin{array}{c}N={=}C{-}NK{-}C{=}N\\|\qquad\qquad|\\N{=}\ C{-}NK{-}C{=}N\end{array}\right\rangle C_6H_4 \qquad\qquad C_6H_4\left\langle\begin{array}{c}N{=}C{-}NH_2\\|\\N{=}C{-}NH_2\end{array}\right. \qquad (138)$$

Dipotassiumfluorubin   2,3-Diaminoquinoxaline
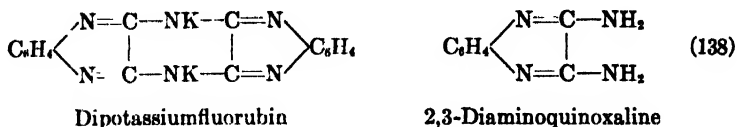
Fluorubin is a product of the nitridation of quinoxaline, since it
may be regarded as derived from two molecules of 2,3-diamino-
quinoxaline by the loss of two molecules of ammonia.   Diamino-
quinoxaline is the ammono diacid ester corresponding to the
ammono dialdehyde-diacetal quinoxaline.

Peterson (278) reports a similar reaction between potassium
amide and toluquinoxaline in liquid ammonia.

2,3-Dimethylquinoxaline and 2,3-dimethyltoluquinoxaline are
reported by Ogg and Bergstrom (276) and by Peterson (278) to
react readily with potassium amide to form the dipotassium salt
of an ammono dienol (dienam) of the probable formula,

$$R\cdot C_6H_3\left\langle\begin{array}{c}NK{-}C{=}CH_2\\|\\NK{-}C{=}CH_2\end{array}\right.$$

R = H or CH_3 in position 6

Ethyl bromide converts these salts to di-n-propyl-quinoxaline or
-toluquinoxaline in a manner similar to that of equation 135.
Di-n-propyltoluquinoxaline reacts with sodium amide to form a
sodium salt (278).

2,3-Diphenylquinoxaline   and   2,3-diphenyltoluquinoxaline,
while sparingly soluble in liquid ammonia at room temperatures,
dissolve easily in potassium amide, presumably to form an addition
compound, in which one or both of the —CH=N— groups has
been converted to —CH(NH—)(NHK).   Further action of po-
tassium amide in ammonia at 130–140°C. produces compounds
which may have the structure of the product of a benzilic acid
rearrangement of the diphenylquinoxalines.

$$R—C_6H_4 \diagdown \begin{matrix} NH—C(C_6H_5)_2 \\ | \\ N=C—NH_2 \end{matrix}$$ (139)
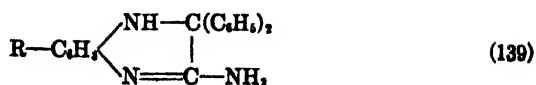
R, in position 6, is H or CH$_3$

E. Acridine and tetrazine

Mesomethyl- and mesobenzyl-acridine react with potassium and sodium amides to form salts of the typical composition,

$$\begin{matrix} C=CHR \\ \diagup \quad \diagdown \\ C_6H_4 \qquad C_6H_4 \\ \diagdown \quad \diagup \\ NK \end{matrix}$$, where R is H or C$_6$H$_5$
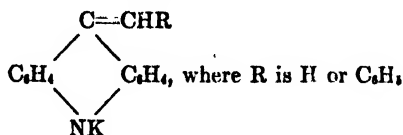
These salts appear to be converted in poor yield by the lower alkyl halides chiefly to N-alkyl-mesomethylenedihydroacridines, in accordance with the equation

$$\begin{matrix} C=CHR \\ \diagup \quad \diagdown \\ C_6H_4 \qquad C_6H_4 \\ \diagdown \quad \diagup \\ NK \end{matrix} + CH_3I \rightarrow \begin{matrix} C=CHR \\ \diagup \quad \diagdown \\ C_6H_4 \qquad C_6H_4 \\ \diagdown \quad \diagup \\ N(CH_3) \end{matrix} + KI$$ (140)
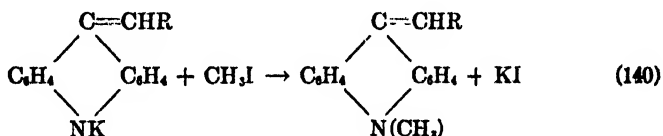
Acridine itself reacts with potassium or barium amides in liquid ammonia to yield a mixture of products which contains ms-aminoacridine (7).

$$\begin{matrix} C—NH_2 \\ \diagup \quad \diagdown\diagdown \\ C_6H_4 \qquad C_6H_4 \\ \diagdown \quad \diagup\diagup \\ N \end{matrix}$$
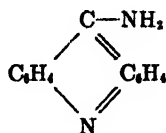
Tetrazine, a crimson colored and somewhat unstable compound, reacts with a liquid ammonia solution of potassium amide at −33°C. to form an insoluble, explosive dipotassium salt, to which either of the following structures may be assigned.

$$CK\diagdown\begin{matrix} N—N \\ \diagdown \\ N=N \end{matrix}\diagup CK \quad \text{or} \quad C\diagdown\begin{matrix} NK—NK \\ \diagdown \\ N \underline{\quad\quad} N \end{matrix}\diagup C$$ (141)
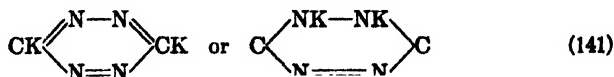
When freshly made, it may be converted by a liquid ammonia solution of ammonium bromide to potassium bromide and tetrazine, but the latter cannot be isolated from specimens of the salt which have stood for a long time at $-33°C.$ or which have been prepared at room temperatures.

The evidence so far obtained does not enable one to distinguish between the two structures of 141, the second of which contains divalent carbon, and is therefore a derivative of ammonocarbonous acid. Perhaps, if the compound is ionic, the two forms of the ion will be in resonance with each other, and it will be meaningless to speak of the structure of the salt (348).

XVIII. ORGANIC COMPOUNDS OF SULFUR

A. Tetraalkylthiodiamines and tetraalkyldithiodiamines

C. K. Clark (99) and G. W. Smith (318) found that the tetraalkyl-thiodiamines and -dithiodiamines of Lengfeld and Stieglitz (246) and of Michaelis (267, 268) are saponified by a liquid ammonia solution of potassium amide, as one might expect in view of the fact that they are the tetraalkyl esters of the ammono acids, $S(=NH)_2$ and $S_2(N=H)_2$ (sulfazylic and thiosulfazylic acids). The decomposition of tetraethylthiodiamine may be represented by the equation

$$S(NEt_2)_2 + 2KNH_2 = S(NHK)_2 + 2Et_2NH \qquad (142)$$

$$Et = C_2H_5$$
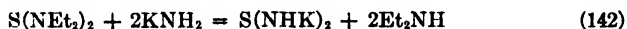
The potassium salt of sulfazylic acid, represented on the right hand side of equation 142, decomposes to some extent into nitrogen and potassium sulfide, so it can not be isolated in a pure state. Potassium thiosulfazylate, $S_2(NHK)_2$, is supposedly formed by the saponification of $S_2(NEt_2)_2$ in accordance with type equation 142, but it can not be isolated because of a further reaction with potassium amide, in which nitrogen and potassium monosulfide are formed. Presumably, potassium sulfazylate, $S(NHK)_2$, is an intermediate in this reaction.

B. Sulfoxides

Schönberg (313) refluxed a solution of diphenyl sulfoxide in toluene with sodium amide for six hours. The only product

isolated from the resulting reaction mixture was diphenylene sulfide, in a 25 per cent yield. Insofar as the formation of this compound is concerned, the sodium amide has acted only as a dehydrating agent, in the sense of the equation

$$C_6H_5\text{---}SO\text{---}C_6H_5 \xrightarrow[-H_2O]{NaNH_2} \begin{array}{c} C_6H_4 \\ | \\ C_6H_4 \end{array}\!\!\!\bigg\rangle S \qquad (143)$$
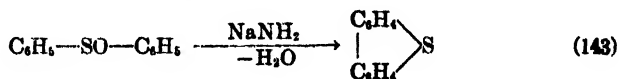
Recently, Courtot, Chaix, and Nicolas (107) have reëxamined this reaction and have improved the yield of diphenylene sulfide to 32 per cent. Smaller quantities of diphenyl sulfide, diphenyl disulfide, and the sodium salt of benzenesulfinic acid were also obtained, together with a very small amount of aniline. Courtot, Chaix, and Kelner (106), in discussing the mechanism of this reaction, conclude that the following equation represents the formation of some of the by-products mentioned above.

$$C_6H_5SOC_6H_5 + NaNH_2 = C_6H_5SONa + C_6H_5NH_2 \qquad (143a)$$

The sodium salt of benzenesulfenic acid, C_6H_5SOH, is unstable, and is either oxidized at the expense of the diphenyl sulfoxide to benzenesulfinic acid, or else undergoes disproportionation to the latter and sodium thiophenate, C_6H_5SNa, which in turn may be converted to diphenyl disulfide by the action of atmospheric oxygen. Diphenyl sulfide apparently results from the removal of an atom of oxygen from diphenyl sulfoxide.

Di-p-bromophenylsulfoxide and di-p-tolylsulfoxide are not dehydrated by sodium amide in the manner of equation 143.

C. Sulfonic acids

Jackson and Wing (228) heated sodium benzenesulfonate with sodium amide in a test tube and obtained about 10 per cent of the amount of aniline theoretically expected from the reaction,

$$C_6H_5SO_2ONa + NaNH_2 = C_6H_5NH_2 \text{ (probably as sodium salt)} + Na_2SO_3 \qquad (144)$$
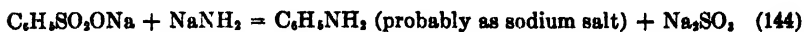
together with a smaller quantity of diphenylamine. As is well known, phenol is formed when sodium benzenesulfonate is fused with sodium hydroxide.

Sachs, in repeating the work of Jackson and Wing, was able to obtain 30 per cent of the theoretical amount of aniline (300).

β-Naphthylamine was obtained in 32 per cent yield by heating sodium naphthalene-β-sulfonate with sodium amide and naphthalene at 200°C. Phenol-p-sulfonic acid is reported to yield none of the expected p-aminophenol under similar conditions (300).

A careful investigation of the action of fused sodium amide on the sodium salt of Schaeffer's Beta Acid (2-naphthol-6-sulfonic acid) in the presence of naphthalene enabled Sachs to obtain as high as 51 per cent of the theoretical amount of 1-amino-6-naphthol. No comment was made concerning the apparent absence of 2-amino-6-naphthol (300). Sodium 2-naphthol-7-sulfonate, fused with naphthalene and sodium amide, is converted to a mixture of aminonaphthols, among which 2-amino-7-naphthol and 1-amino-6-naphthol were identified. The two compounds together were formed in 57 per cent yield (300). Sodium 2-naphthol-8-sulfonate is changed under similar conditions to a mixture of aminonaphthols, the chief constituent of which is 1-amino-6-naphthol (300). Disodium 2-naphthol-1-sulfonate apparently yields only a single product, which was however not identified with any of the known aminonaphthols (300). Sodium 1-naphthol-5- and -8-sulfonates are converted to the expected aminonaphthols (300). Naphtholdisulfonic acids R (2,3,6) and G (2,6,8) gave products of an indefinite nature. Anthraquinone-β-sulfonic acid gave a small yield of anthraquinone, together with an unidentified substance that appeared to be an aminoanthraquinone (300).

The investigations of Sachs indicate that molecular rearrangements may occur in the fusion of the naphtholsulfonic acids with sodium amide. This is not surprising in view of the experiments of Meharg and Allen (258) and of Button (77), who have observed molecular rearrangements in the hydrolysis of the chlorotoluenes with aqueous alkali at high temperatures.

D. Thionaphthene

Weissgerber and Kruber (341) have utilized sodium amide in the separation of thionaphthene,

$$C_6H_4 \overbrace{\underbrace{}_{S}}^{\displaystyle \begin{array}{c} CH \\ \diagdown\diagdown \\ CH \end{array}}$$
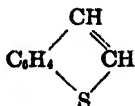
from crude naphthalene, or from the enriched concentrates containing a larger proportion of the sulfur compound. Thionaphthene itself reacts with sodium amide under xylene at temperatures from about 60°C. to 120°C. to form a yellow brown sodium salt, which is decomposed by water with regeneration of the thionaphthene. In order to find out which hydrogen atoms were replaced by sodium in the formation of this salt, an experiment was performed in which 400 grams of thionaphthene was heated at 100–145°C. with 3.75 equivalents of sodium amide under xylene, dry carbon dioxide then being passed through the mixture for some time at 100–110°C. After methylation of the reaction product, approximately equal quantities of the methyl esters of thionaphthene-2-carboxylic acid and thionaphthene-2,3-dicarboxylic acid were obtained, indicating that some disodium thionaphthene was formed under these conditions.

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(17) Reference 14, pp. 353–7.

(18) BAUER: Ann. chim. [9] **1**, 393–437 (1914).

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(19) Reference 18, pp. 397 -8.

(20) Reference 18, pp. 406–8.

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THE DETERMINATION OF THE STRUCTURE OF ROTENONE

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About three-quarters of a century ago travelers in the East Indies, South America, and tropical Africa reported the use of certain plants as an aid in catching fish. Botanists have since shown that some of the most potent of these fish-poisoning plants, commonly called tuba, timbo, cubé, and haiari, belong to the family *Fabaceae*, or *Papilionaceae*, and the genera *Derris*, *Milletia*, *Tephrosia*, and *Lonchocarpus*. These genera owe their toxic properties to one or more chemically closely related substances, of which the most important is rotenone.

The employment of derris extract as an insecticide by gardeners in the East Indies has long been a common practice. As early as 1848 Oxley (34) reported the use of tuba root (*D. elliptica*) for this purpose in connection with nutmeg cultivation. A number of related species have since been found to have insecticidal value.

Recent studies have shown that, although rotenone and other fish poisons have a strong toxic action when introduced into the blood stream of warm-blooded animals, they are relatively nontoxic when taken by mouth (1).

In the last few years there has been an increasing use of derris products as insecticides, and the plant is now cultivated in the Dutch East Indies and the Malay States. Derris root and its concentrated extracts, as well as rotenone itself, are now articles of commerce.

It appears that rotenone was first isolated in 1895 by Geoffroy (8) from a plant native to French Guiana and called *Robinia nicou*. The substance was reported to melt at 162°C. and was named by the author nicouline. Tests which the author de-

scribed in detail were made with nicouline on several insects and also on warm-blooded animals. The same plant, now called *Lonchocarpus nicou*, has since been shown to contain rotenone (6), which is therefore identical with Geoffroy's nicouline.

Kazuo Nagai in 1902 isolated from the roots of *Derris chinensis* a crystalline substance, melting at 163°C., which he called rotenone (33). He attempted to determine its molecular weight and prepared the phenylhydrazone.

·In 1911 Lenz (32) extracted from *Derris elliptica* a compound reported to melt at 158°C. and named it derrin; five years later Ishikawa (18) isolated the identical substance from the same plant and observed that it was optically active. He gave it the name tubatoxin. In the later literature the name rotenone has been generally accepted.

Kariyone (19) observed the presence of methoxyl in rotenone and established the presence of one unsaturated linkage by its catalytic reduction to dihydrorotenone. He also prepared the oximes of rotenone and dihydrorotenone and made the important observation that rotenone was cleaved by alkali and yielded an acid of the formula $C_{12}H_{12}O_4$ (20), which he called tubaic acid. Tubaic acid was shown to contain one double linkage and gave the color reactions of a phenol. By alkali fusion it was converted into the isomeric isotubaic (rotenic) acid (42, 11). Dihydrorotenone yielded dihydrotubaic acid, identical with the reduction product of tubaic acid (20).

Takei (42) found that rotenone could be isomerized to isorotenone, and that by mild oxidation it yielded a yellow derivative, later shown to be dehydrorotenone. By energetic oxidation he prepared rotenonone and converted it into a hydroxy acid. The correct empirical formula for rotenone, $C_{23}H_{22}O_6$, was first proposed by Butenandt (2) in his inaugural dissertation, and this formula was confirmed by Takei (43).

In 1928 Butenandt (3) published an article on rotenone, in which he reported the following observations. Of the six oxygen atoms of rotenone, two are present in the form of methoxyl groups and another as a carbonyl group, while the other three cannot be directly detected. It was suspected that one of these

was in the form of an indifferent ether linkage, while certain reactions indicated that the remaining two were in the form of a lactone group.[1] By energetic reduction, both the unsaturated linkage and the ketone group can be reduced and the resulting dihydrodesoxyrotenone, $C_{23}H_{26}O_5$, can be calculated to be derived from the hydrocarbon $C_{21}H_{28}$. From the hydrogen content of a hydrocarbon of this formula, it can be assumed that two benzene rings are present in rotenone, and the remarkable stability of dihydrodesoxyrotenone indicates that all carbon atoms are directly connected with each other.

If rotenone is allowed to react with hydroxylamine or hydrazine in alkaline solution, the resulting derivatives are isomeric with those prepared in acid or neutral solutions, and exhibit the properties of phenols.

By treatment with zinc dust and alkali in alcoholic solution, rotenone yields two products, one of which, derritol, is alkali-soluble, is represented by the formula $C_{21}H_{22}O_6$, and gives the reactions of a phenol. The other compound, which has been called rotenol, is alkali-insoluble, and is represented by the formula $C_{23}H_{24}O_6$.

A number of oxidizing agents easily convert rotenone into dehydrorotenone, a yellow compound of formula $C_{23}H_{20}O_6$. Unlike rotenone, dehydrorotenone is not cleaved by alkali but is converted with addition of two moles of water into derrisic acid of the formula $C_{23}H_{24}O_8$.

The observations briefly described above have proved to be of special importance as a basis for subsequent work on the part of three groups of investigators, work which led to the determination of the complete structure of rotenone and of practically all

[1] The evidence for the presence of a lactone group was seen in the formation of derrisic acid by hydrolysis of dehydrorotenone and in the formation of alkali-soluble products obtained by hydrogenation of various rotenone derivatives. These results have since been explained on the basis of certain secondary reactions, but the lactone theory became firmly established in the earlier stages of the investigations and caused much confusion in the speculations on the structure of rotenone and its derivatives. It was finally abandoned after it was found that all the oxygen atoms, with the exception of the one contained in the carbonyl group, are present as ether linkages.

of its derivatives.   The structure for rotenone now unreservedly accepted is expressed by formula I (24, 5, 50).
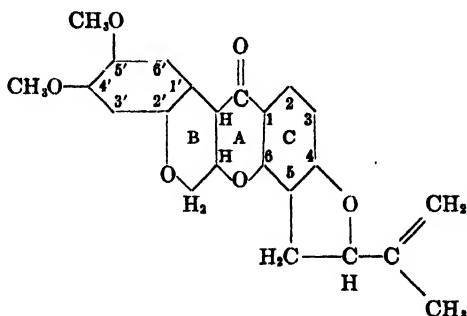
This formula consists of three characteristic systems,—a central dihydro-γ-pyrone (A), combined on the one hand with a dihydrobenzopyran (B), and on the other with a dihydrobenzofuran system (C).   On the basis of this formula, all well-defined reactions of rotenone can be easily explained.   The characteristic rotenone derivatives, which will be discussed in detail, result from reactions which are characteristic of the one or the other of these systems, and are for the most part supported by analogies with other compounds containing the same groupings.

REACTIONS INVOLVING THE DIHYDROBENZOFURAN SYSTEM

The first cleavage product obtained from rotenone was tubaic acid, the formula (II) of which has been determined by an extensive series of investigations.
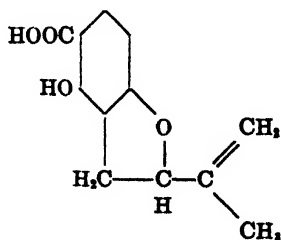
II

Tubaic acid was shown by Kariyone to be an optically active monobasic phenolic acid of the formula $C_{12}H_{12}O_4$, containing an indifferent oxygen atom and one double linkage which was demonstrated by its catalytic reduction to dihydrotubaic acid (20). On fusion with alkali it is converted into the optically inactive isotubaic (rotenic) acid (42).

Tubaic, dihydro- and iso-tubaic acids when heated above their melting points lose carbon dioxide and are converted into the corresponding phenols (43, 44) from which the acids can be regenerated by the action of alkali bicarbonates (44). The phenolic hydroxyl group in the acids can be acetylated, and by means of diazomethane its methylation can be accomplished, although only with great difficulty (43).

Both dihydro- and iso-tubaic acids yield isobutyric acid on oxidation with permanganate, while tubaic acid yields only acetic acid (43, 44).

Isotubanol (roteol), the phenol corresponding to isotubaic (rotenic) acid, gives resorcinol together with isovaleric acid on drastic alkali fusion (46).

Isotubaic acid is not easily hydrogenated. It is possible, however, under energetic conditions, to add one mole of hydrogen to it forming dihydroisotubaic acid. Dihydroisotubaic acid has been shown to be a racemic mixture which can be separated into its enantiomorphs, of which the levo form is identical with dihydrotubaic acid (4, 46).

The transformations of tubaic acid so far referred to indicated that it might best be represented as a hydroxydihydrocumaroncarboxylic acid with an isopropenyl side chain (43). The resistance of the phenolic hydroxyl toward methylation indicated that it was diortho-substituted (48, 17).

By drastic hydrogenation of tubaic acid, a tetrahydrotubaic acid is obtained, together with dihydrotubaic acid (16). If the hydrogenation of tubaic acid is carried out in alkaline solution, an intermediary compound, isodihydrotubaic acid, isomeric with dihydrotubaic acid is obtained, which is easily further reduced in neutral solution to tetrahydrotubaic acid (49). Tetrahydrotubaic acid is optically inactive (16). It contains two phenolic

hydroxyl groups, both of which are easily acetylated. One of the acetyl groups of the diacetyl compound is easily removed by alcoholic potassium acetate solution, leaving a monoacetyl compound (17). Of the two hydroxyl groups in tetrahydrotubaic acid, only one is easily methylated (17). Tetrahydrotubaic acid is decarboxylated to a substituted dihydroxybenzene (16), which on oxidation yields isocaproic acid (50).

Owing to the properties of the hydroxyl group of tubaic acid and also with reference to certain derivatives which contain the groupings of tubaic acid in which the corresponding phenol group is free, it can be assumed that the original phenolic hydroxyl group is diortho-substituted (48, 17). Tetrahydrotubanol is therefore 2-isoamylresorcinol as represented by formula III (16, 17). This formula has lately been confirmed by synthesis (10a).

$$\text{HO}\!\!\bigcirc\!\!\text{OH}$$

$$\text{H}_2\text{C}\text{---}\underset{\text{H}_2}{\text{C}}\text{---}\underset{\text{H}}{\text{C}}\overset{\text{CH}_3}{\underset{\text{CH}_3}{\diagdown}}$$
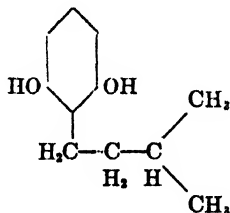
III

Tubanol is expressed by formula IV.

$$\text{HO}$$
$$\text{H}_3\text{C}\text{---}\underset{\text{H}}{\text{C}}\text{---}\text{C}\overset{\text{CH}_2}{\underset{\text{CH}_3}{\diagdown}}$$
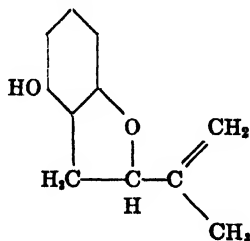
IV

Formula II satisfactorily explains all the transformations of tubaic acid. Its isomerization is due to the migration of the double bond from the side chain into the ring, and isotubaic acid

is therefore expressed by formula V; this formula has been confirmed by synthesis (34a).

V
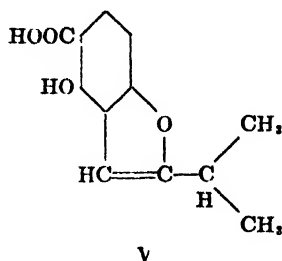
When tubaic acid (II) is reduced to dihydrotubaic acid, the double bond in the side chain is saturated, with the formation of the optically active dihydrotubaic acid of formula VI.

VI
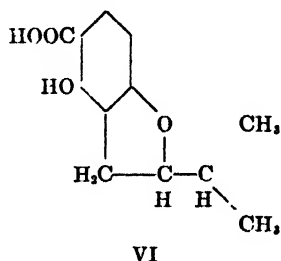
Isotubaic acid (V) is reduced to racemic dihydrotubaic acid, which can be separated into the two active forms. The levo form is identical with the natural active dihydrotubaic acid.

The hydrogenation of tubaic acid also takes place in another manner, with opening of the oxide ring involving the loss of an asymmetric center, followed by reduction of the double bond, and results in the formation of tetrahydrotubaic acid of formula VII (16, 17).

VII
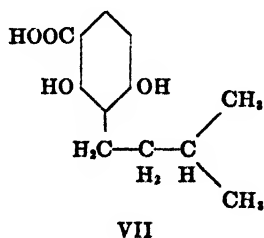
If the hydrogenation is carried out in alkaline solution, the oxide ring is opened without reduction of the double bond, which probably shifts to the 2, 3-position, and the intermediary product, isodihydrotubaic acid (VIII), can be isolated (49).

$$\text{HOOC}$$
$$\text{HO} \qquad \text{OH} \qquad CH_3$$
$$H_2C—C{=}C$$
$$\qquad\quad H \qquad CH_3$$

VIII
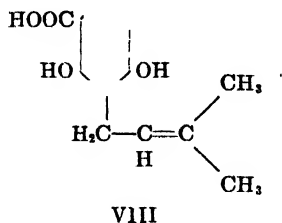
On further hydrogenation in neutral solution, isodihydrotubaic acid yields tetrahydrotubaic acid (VII). The behavior of tubaic acid on hydrogenation has a striking analogy with that of a number of codein derivatives, of which the following is an example. Desoxycodein-C of formula IX is hydrogenated to β-tetrahydrodesoxycodein (38) of formula X. The groupings involved are analogous to those present in tubaic acid (II), the formula of which may be written also as shown in formula XI.

$$N—CH_3 \qquad\qquad\qquad\qquad N—CH_3$$
$$HH_2 \quad CH_2 \qquad\qquad\qquad H_2 \quad CH_2$$
$$\qquad\qquad H_2 \qquad\qquad\qquad\qquad\qquad H_2$$
$$\qquad CH_3 \quad H + 2H_2 \rightarrow \qquad\qquad CH_3$$
$$\qquad H \ H \qquad\qquad\qquad\qquad H_2 \ H_2$$
$$CH_3O \qquad\qquad\qquad\qquad CH_3O \quad OH$$
$$\qquad O$$

X

$$HOOC \quad OH$$
$$\qquad\qquad\qquad H_2 \qquad CH_2$$
$$\qquad\qquad\qquad C—C$$
$$\qquad\qquad\qquad H$$
$$\qquad\qquad O \qquad CH_3$$

XI
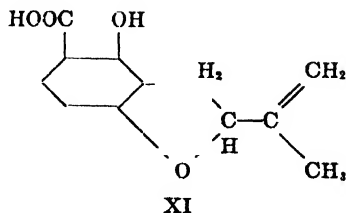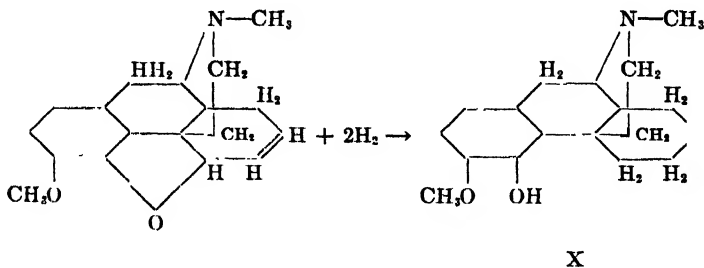
On hydrogenation of both compounds the oxide ring is opened and phenolic compounds are formed.

According to the theory of Schöpf (37), the grouping concerned,
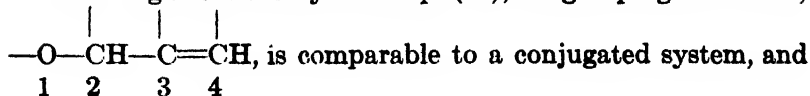
$$-\underset{1}{O}-\underset{2}{\overset{|}{C}H}-\underset{3}{\overset{|}{C}}\!\!=\!\!\underset{4}{\overset{|}{C}H},$$ is comparable to a conjugated system, and hydrogenation takes place with the opening of the ether ring. This reaction is explained by the assumption that a 1, 4 addition of hydrogen (at $-O-$ and C_4) first takes place, followed by the formation of a double bond at 2, 3.   This double bond may be further reduced to the tetrahydro derivative, as in the case of the codein derivatives and tetrahydrotubaic acid, but remains unsaturated in isodihydrotubaic acid (VIII), which therefore contains the grouping,

$$-CH_2CH\!=\!C\underset{\diagdown}{\overset{\diagup}{}}\!\!\!\begin{matrix}CH_3\\[4pt]CH_3\end{matrix}$$
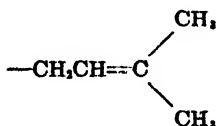
When the 2-isoamylresorcinol (III) formed by the decarboxylation of tetrahydrotubaic acid is oxidized, the resorcinol is destroyed and isocaproic acid can be isolated from the reaction products.

All these reactions, which are characteristic of the dihydrobenzofuran system of tubaic acid, find their parallel in those rotenone derivatives in which this grouping is present.

THE ISOMERIZATION OF ROTENONE AND OF THOSE OF ITS DERIVATIVES WHICH CONTAIN THE ISOPROPENYL SIDE CHAIN

When rotenone is treated with strong acids, it is converted into isorotenone (XII) (5, 42, 10).
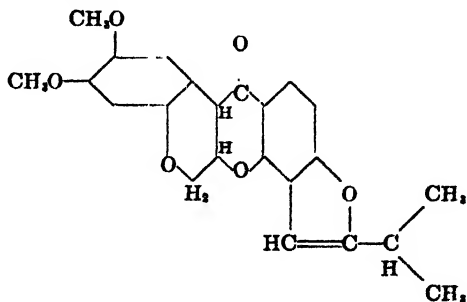
XII

The reaction involved is the same as that which takes place when tubaic acid is converted into isotubaic (rotenic) acid.   Like isotubaic acid, isorotenone is not readily reduced by catalytic hydrogenation.   On cleavage with alcoholic alkali, isotubaic acid is obtained instead of tubaic acid (45, 4, 11).

All rotenone derivatives which contain the isopropenyl side chain are converted by strong acid into the corresponding iso-derivatives (4), which in turn yield isotubaic acid.   Isorotenone shows all the characteristic reactions which are concerned with changes in the dihydro-γ-pyrone and dihydrobenzopyran systems.   For example, isoderritol and isorotenol (27), isodehydro-rotenone (29, 4), and isoderrisic acid (4) are obtained from isoro-tenone itself by suitable processes as well as by isomerization of the normal compounds with the unsaturated side chain (4), and isorotenonone is obtained by oxidation of isorotenone (50).

As will be shown below, two asymmetric centers are lost in the formation of the dehydro compounds and the derritols.   Since another asymmetric center disappears in the formation of the iso compounds, isodehydrorotenone, isoderrisic acid (4), and isoderritol (15) are optically inactive.

HYDROGENATION PRODUCTS OF ROTENONE

When rotenone is reduced with catalytic hydrogen the main product of the reaction is dihydrorotenone (XIII) (20, 27).
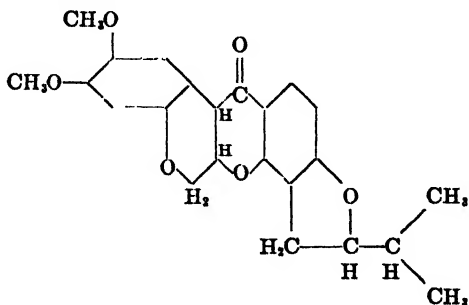
XIII

Dihydrorotenone usually melts at 216°C., but it occurs in di-morphic form, the unstable modification of which melts at 164°C. (26).   It contains no double bond in the side chain and is there-

fore not isomerized by acids, but it gives all the reactions characteristic of the dihydrobenzopyran and dihydro-γ-pyrone systems.

Dihydrorotenone, and also rotenone, yield a monoacetyl derivative when treated with sodium acetate and acetic anhydride. These compounds are the enol type of acetates (41) as is shown by their behavior on hydrogenation. Acetyldihydrorotenone is reduced by catalytic hydrogenation to dihydrodesoxyrotenone (41).

The dihydro derivatives are obtained from dihydrorotenone by the same processes by which the corresponding unsaturated compounds are obtained from rotenone. Thus dihydrorotenone yields dihydroderritol, dihydrorotenol (27), and dehydrodihydrorotenone (29). All rotenone derivatives containing the unsaturated side chain yield corresponding dihydro compounds by hydrogenation.

When the dihydro compounds are prepared by hydrogenation, the reaction proceeds in part with opening of the oxide ring, as in the case of tubaic acid, with the resultant loss of an asymmetric center and formation of phenolic derivatives (27, 15). The reduction takes the latter course, especially in alkaline solution. In some cases the unsaturated phenol can be isolated. Rotenone itself is thus hydrogenated in neutral solution to a mixture of dihydrorotenone and rotenonic acid (XIV) (27, 10),[2] the latter being a phenol corresponding to isodihydrotubaic acid (VIII).
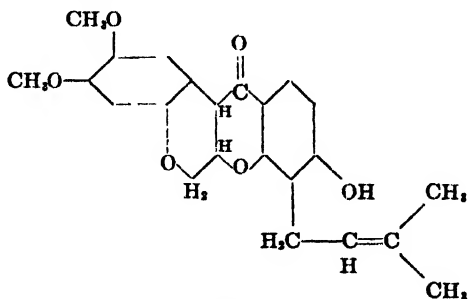
XIV

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[2] These phenolic derivatives were formerly thought to be acids arising from the opening of a lactone group and in some instances the term "acid" has been retained.

The double bond may be further reduced, with the formation of dihydrorotenonic acid (tetrahydrorotenone) containing the saturated side chain,

$$-CH_2-CH_2-CH \begin{cases} CH_3 \\ CH_3 \end{cases}$$
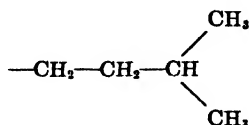
Dihydrorotenonic acid (tetrahydrorotenone) therefore differs from rotenonic acid only by having a saturated side chain.

When dihydrorotenonic acid is boiled with acetic anhydride and sodium acetate the resulting product is a diacetyl compound (41). This result is explained by the assumption that this compound, like rotenone and dihydrorotenone, reacts to form an enol acetate. One of the acetyl groups in dihydrorotenonic acid is therefore of the enol acetate type, whereas the other results from the acetylation of the phenol group. Tetrahydro derivatives of all the characteristic rotenone derivatives have been obtained by hydrogenation (16, 24, 28, 29, 31). All of these are phenols, soluble in alkali.

It is of special importance that with the reductive cleavage of the oxide ring of the benzofuran system an asymmetric center is lost (15). If this reductive cleavage is associated with a reaction involving the loss of the asymmetric centers of the dihydro-γ-pyrone system, the resulting compounds are inactive (4, 15). Tetrahydromethylderritol (methyldihydroderritolic acid) (XXVI) and tetrahydrodehydrorotenone   (dehydrodihydrorotenonic   acid) (XXXII) are, for example, inactive (15).

Rotenonic acid (XIV) undergoes a rearrangement when treated with sulfuric acid whereby it is converted into β-dihydrorotenone (XV), (9, 10), containing the chroman in place of the dihydrobenzofuran system.
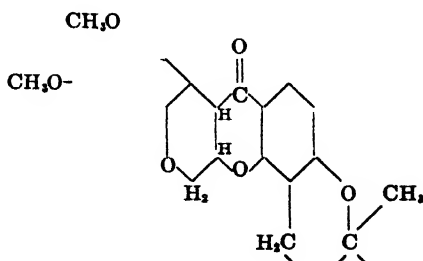
This reaction is in a measure comparable to the conversion of an unsaturated acid into a saturated lactone and involves a ring closure with disappearance of the phenol group and the double bond. β-Dihydrorotenone exhibits those reactions characteristic of the dihydro-γ-pyrone system and is cleaved by alkali, with the formation of β-dihydrotubaic acid of the probable formula XVI (9, 10, 5).

HOOC

HO

O   CH$_3$

H$_2$C   C

C   CH$_3$

H$_2$
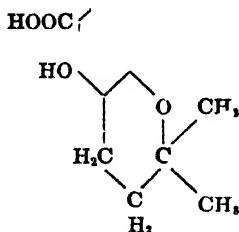
XVI

The corresponding dehydro derivative has been prepared from β-dihydrorotenone and is hydrolyzed by alkali to β-dihydroderrisic acid, which in turn has been oxidized to derric acid (9).

Derrisic acid is also hydrogenated to the corresponding tetra-hydro derivative, which, owing to its importance in connection with dehydrorotenone, will be discussed more fully under a separate heading.

REACTIONS INVOLVING THE DIHYDROBENZO-γ-PYRONE SYSTEM

The dihydrobenzo-γ-pyrone ring is responsible for the instability of rotenone, and those of its derivatives which contain this grouping, toward alkali.   Those derivatives in which this grouping is absent are much more stable in alkaline solution.   By the action of alcoholic alkali rotenone is quickly decomposed, with the formation of large quantities of uncrystallizable resins.   From these a small yield of tubaic acid is obtained (20, 42, 44, 12).

CH$_3$O

CH$_3$O

O

C

H   OR

H   B$^-$

O

H$_2$

O   CH$_2$

H$_2$C   C   C
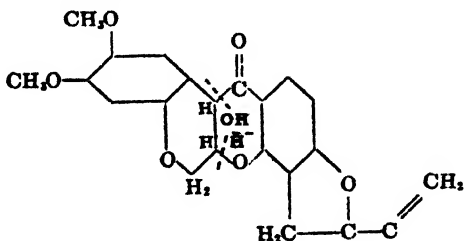
It seems very probable that the first point of attack involves the hydrolysis of the oxidic linkage of the dihydrobenzo-γ-pyrone ring (4).   Under ordinary conditions in the presence of air this reaction is followed to a certain extent by cleavage at the carbonyl group, with the formation of tubaic acid as shown in formula XVII.

Derritol

When the alkaline cleavage is carried out under reducing conditions, as in the presence of zinc, the main products are derritol and rotenol (2, 3).   These derivatives have proved to be of special importance in determining the structure of rotenone.

The empirical formula ($C_{21}H_{22}O_6$) for derritol as determined by Butenandt (3) differs from that of rotenone in that it contains two carbon atoms less than the parent substance.   It is separated from the rotenol, which is simultaneously formed in the process, by means of alkali, in which the rotenol is nearly insoluble.   The corresponding iso- and dihydro-derritols were later prepared from iso- and dihydro-rotenone by the same process.   Isoderritol is optically inactive, whereas the other two are active (15).   Derritol contains the two methoxyl groups and the carbonyl group originally present in rotenone.   The presence of a phenolic hydroxyl group was indicated by its solubility in alkali as well as by the color reaction with ferric chloride.   The presence of a second hydroxyl group was indicated by the Zerewitinoff method (3).   From these facts it was suggested by Butenandt that derritol possibly contained the grouping XVIII, resulting from reduction and hydrolysis of the grouping XIX (3).
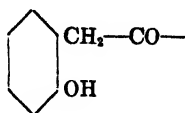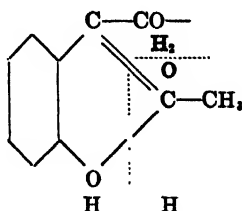
XVIII   XIX

Of the two hydroxyl groups of derritol, only one is easily methylated.   The resulting derritol monomethyl ether (XXV) (28) is hydrogenated to the alkali-soluble tetrahydromethylderritol (XXVI) (28), which is oxidized by hydrogen peroxide to a trimethoxyphenylacetic acid (39).   The trimethoxyphenylacetic acid has been oxidized to its next lower homologue, which is identical with asaronic acid or 2, 4, 5-trimethoxybenzoic acid (40).   The structure of the 2, 4, 5-trimethoxyphenylacetic acid, (homoasaronic acid) (XX) has also been established by synthesis (50).

$$CH_3O \overset{6}{\underset{5}{\bigcirc}} \overset{1}{CH_2COOH}$$
$$CH_3O \underset{4}{\underset{3}{\bigcirc}} \overset{2}{OCH_3}$$

XX
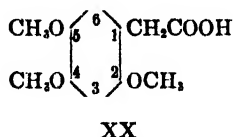
When derritol itself is oxidized with permanganate in acetone solution, 2-hydroxy-4, 5-dimethoxybenzoic acid (40) is obtained, the structure of which (XXI) has been established by Clark (7) as well as confirmed by synthesis (50, 35).

$$CH_3O - \bigcirc - COOH$$
$$CH_3O - - OH$$

XXI
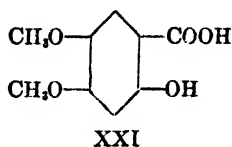
From these facts it follows that derritol contains the grouping XXII.

$$CH_3O - \langle \quad \rangle - CH_2CO -$$
$$CH_3O - \langle \quad \rangle - OH$$

XXII
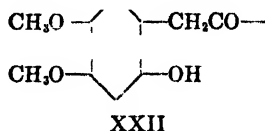
By alkali fusion derritol yields isotubaic acid[a] (13), and by permanganate oxidation, tubaic acid (48).   Isotubaic and dihydrotubaic acids are likewise obtained from iso- and dihydro-derritols

[a] Under the conditions of alkali fusion the tubaic acid grouping is converted into the isotubaic acid structure.

(13).   The foregoing facts establish the formula for derritol as XXIII.

O

CH₃O—⟨   ⟩—CH₂—C—

CH₃O-   ⌐—OH HO—

O   CH₂

H₂C—C—C

H

CH₃
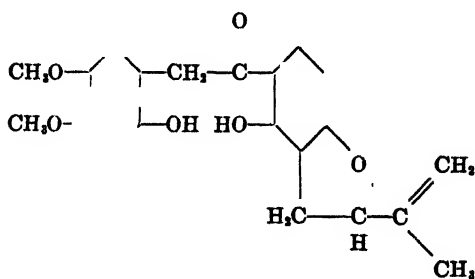
XXIII

The mechanism of the reactions leading to the formation of derritol is best explained by the following series of reactions (24):

O
‖
C

H
C
HC

CH₃

O

Rotenone

+ H₂O

O
H
HCOH
CH₂ HO
O

XXIV

− H₂O

O
C̈
C
CH
ĊH₂ HO
O

XXIV-A

O
‖
C
C
H₂O CH
ĊH₂ HO
O
H   H
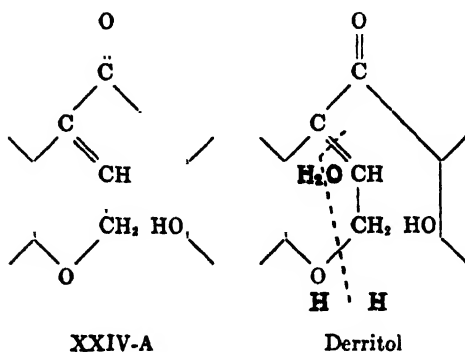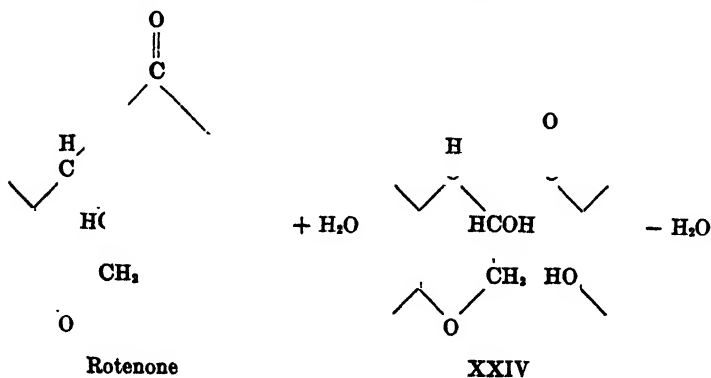
Derritol

Derritol methyl ether is therefore represented by formula XXV.
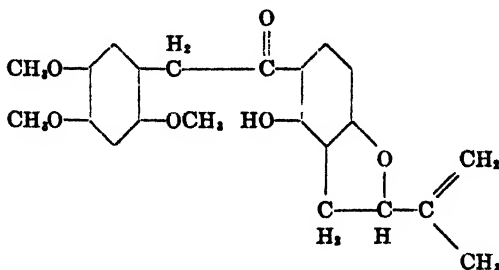
XXV

The hydroxyl group attached to the tubaic acid part of the derritol molecule is resistant to methylation and is of such weak acidic properties that its hydrogen is not replaced by alkali metals. Consequently, derritol methyl ether (XXV) is not soluble in alkali, although it gives a color reaction with ferric chloride. Derritol methyl ether is oxidized by hydrogen peroxide at the carbonyl group to homoasaronic acid.[4] Tetrahydromethylderritol (XXVI) has been synthesized from tetrahydrotubanol (III) and homoasaronic acid (XX) by condensation with zinc chloride (50).
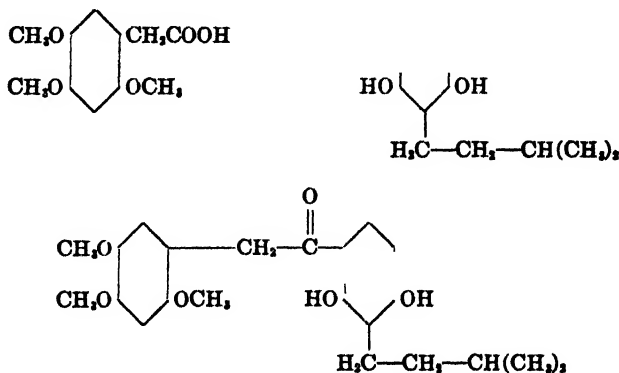
XXVI

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[4] All aromatic aldehydes and ketones having a phenolic hydroxyl group in the ortho or para position are oxidized by hydrogen peroxide to polyphenols without the formation of a substituted benzoic acid (17).

The derritols are easily dehydrated (3, 41) and the resulting anhydroderritols which contain the grouping XXVII are also

XXVII
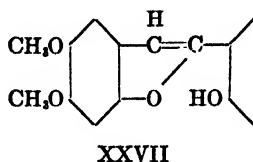
insoluble in alkali, but give the ferric chloride color reaction and yield monoacetyl derivatives.

Rotenol

Rotenol is obtained, together with derritol, by zinc alkali reduction of rotenone (3), and corresponding compounds are obtained from iso- and dihydro-rotenone (27). It was at first supposed that rotenol was the alcohol corresponding to rotenone (3) because no ketone derivatives of rotenol could be obtained by the usual methods. Evidence for the presence of the carbonyl group was furnished by the fact that isorotenol, which differs from rotenol only in the arrangement of the benzofuran system, was reduced by Clemmenson's method to desoxyisorotenol (14). Later Takei succeeded in obtaining an oxime from rotenol (49). By peroxide oxidation rotenol, or the corresponding tetrahydro-rotenol (dihydrorotenolic acid), yields netoric acid $C_{12}H_{14}O_6$ (5, 39), in all probability to be represented by the formula XXVIII (25).

XXVIII
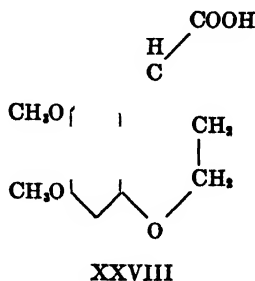
Rotenol yields isotubaic acid on alkali fusion in much larger quantities than any other rotenone derivative (13). Both derri-

tol methyl ether and rotenol give all the characteristic reactions (isomerization to iso derivatives, cleavage of the oxide ring on hydrogenation, with loss of an asymmetric center and formation of a phenolic hydroxyl group and reduction to dihydro and tetrahydro derivatives) of those rotenone derivatives which are concerned with the dihydrobenzofuran system.

By the action of alkaline ferricyanide, a dehydrorotenol (14, 10, 25) is obtained which is isomeric with rotenone, and which is easily reconverted into rotenol by zinc alkali reduction. The structure of dehydrorotenol is as yet unexplained, but it seems to be unrelated to dehydrorotenone.

Rotenol results from the reduction of the unsaturated intermediary product (XXIV-A), which is formed with loss of an asymmetric center and is represented by the formula XXIX.
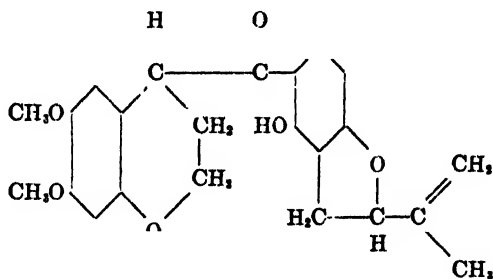
XXIX

Corresponding formulas with suitable arrangements in the benzofuran nucleus apply to its derivatives, iso-, dihydro-, and tetrahydro-rotenol. Isorotenol and tetrahydrorotenol, which have no other asymmetric center, are therefore racemic mixtures.

ISOMERIC CARBONYL DERIVATIVES OF ROTENONE

Two types of carbonyl derivatives are obtained from rotenone. When its oxime or hydrazone is prepared in acid solution the normal derivatives are obtained. If, however, the reaction is carried out in alkaline solution, isomeric compounds result which are soluble in alkali and exhibit the properties of phenols (3).

The formation of these phenolic carbonyl derivatives is best

explained with the assumption that the oxidic linkage of the dihydrobenzo-γ-pyrone system is first hydrolyzed, as is represented by the first step in the formation of derritol and rotenol. The carbonyl derivative of the intermediary compound of formula XXIV then rearranges, with loss of one mole of water to form the phenolic isocarbonyl derivative (XXX).

The reactions resulting in the formation of rotenone isoxime may be illustrated as follows:

```
        O                               O
   H    ‖                          H    ‖
   C————C-                         C————C-
      HC—O-          \   + H₂O        HCOH  HO\        + NH₂OH
         |             \  ————————          |            ————————→
         CH₂                                CH₂            − 2H₂O
      /                              /
   O                                O

   Rotenone                            XXIV


               H
               C————C————
            \ /   \      \
             HC—N  HO\
                 |
                 CH₃
              /  /
           O

              XXX
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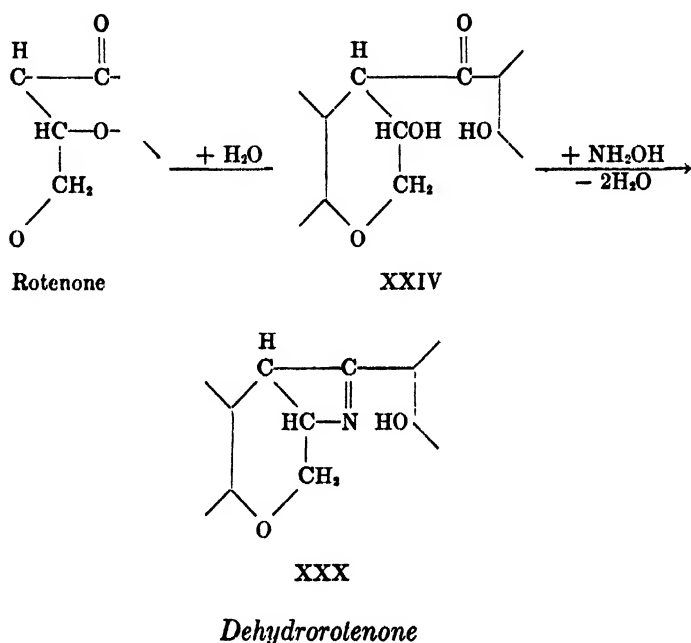
Dehydrorotenone

A number of mild oxidizing agents convert rotenone into dehydrorotenone with the loss of two hydrogen atoms from the dihydro-γ-pyrone system, and corresponding dehydro compounds are obtained from all derivatives which contain the dihydro-γ-pyrone system, for example, from isorotenone (XII), dihydrorotenone (XIII), and β-dihydrorotenone (XV).

For reasons which will be presented dehydrorotenone is expressed by formula XXXI (24, 5, 50, 36).

CH₃O

CH₃O—

O

C

H₂

O   O

CH₃

H₂C———C—C

H

CH₃
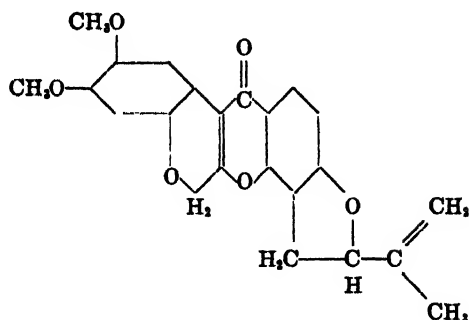
XXXI

Dehydrorotenone is optically active, but isodehydrorotenone is inactive (3). Since it has already been demonstrated that an asymmetric center is lost in the process of isomerization, it is apparent that the remaining asymmetric centers are lost in the formation of the dehydro compounds. The combination of the two reactions leads to an optically inactive compound (3). Similarly the catalytic reduction of dehydrorotenone with opening of the oxidic linkage of the dihydrobenzofuran grouping, a reaction which also involves the loss of a center of optical activity, leads to an optically inactive compound, dehydrodihydrorotenonic acid[5] (tetrahydrodehydrorotenone) (XXXII) (15).

CH₃O

CH₃O—

O

C

O   O

H₂

—OH

CH₃

H₂C—CH₂—CH

CH₃
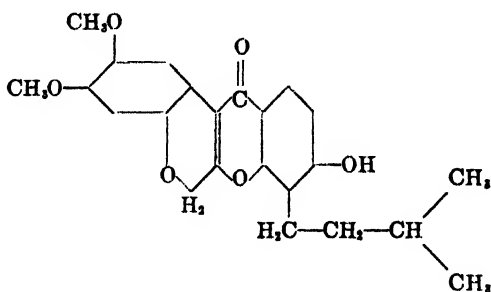
XXXII

The most convenient method for preparing the dehydro compounds is by the action of iodine and alkali acetate on an alcoholic

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[5] It has not been possible by any means to reduce the double bond in the γ-pyrone system of dehydrorotenone.

solution of rotenone, iso- or dihydro-rotenone (3, 27). Some of the dehydro compound is obtained directly, but the main product of the reaction consists of the acetate of a hydroxy derivative (27). By this process, rotenone yields acetylrotenolone. Rotenolone, obtained on saponification of the acetyl compound, is represented by the formula $C_{23}H_{22}O_7$, and is to be regarded as a hydroxyrotenone. Its formation is explained by a process of iodine substitution at one of the labile hydrogen atoms of the dihydro-γ-pyrone system, followed by reaction of the iodo compound with the alkali acetate.

Rotenolone, which is represented by the formula XXXIII,[6] is easily dehydrated by alcoholic sulfuric acid to dehydrorotenone (XXXI) (27).
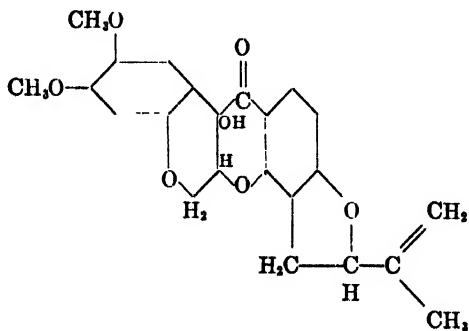
XXXIII

Corresponding formulas apply to iso-, dihydro- (27), and β-dihydrorotenolone (9), all of which have been obtained by the same process.

Dehydrorotenone is converted by alcoholic alkali, or zinc and alkali with addition of two molecules of water, into derrisic acid of formula XXXIV (3, 24).

---

[6] It is possible that the hydroxyl group is on the other asymmetric carbon atom of the dihydro-γ-pyrone ring and there also exists the possibility of cis-trans isomerism. Either of these theories could explain the existence of the isomeric rotenolone derivatives which have been observed (31).

XXXI

XXXIV
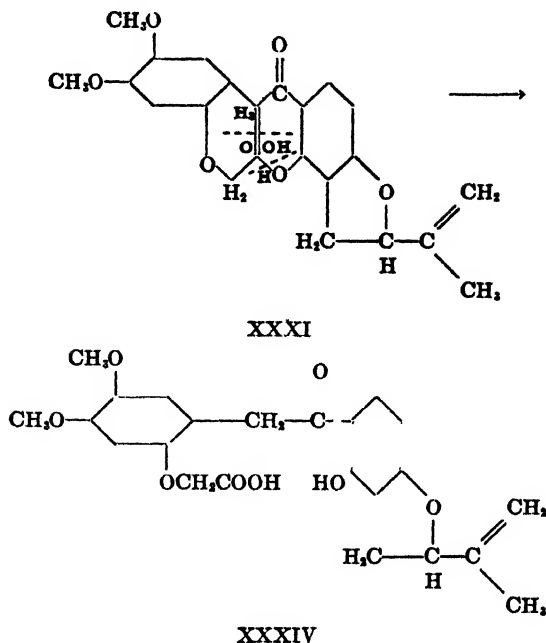
Derrisic acid stands in close relation to derritol (XXIII).   Its ethyl ester is obtained by substitution of the $CH_2COOC_2H_5$ group on the reactive phenol hydroxyl (25).   It has been shown to contain a free phenol group which gives a color reaction with ferric chloride, and which may be acetylated (3).   Iso- and dihydro-derrisic acids are obtained by the same reaction from iso- and dihydro-derritol.

Like all rotenone derivatives containing the dihydrobenzo-γ-furan grouping with the unsaturated side chain, derrisic acid is hydrogenated to tetrahydroderrisic acid of the formula **XXXV** (24).
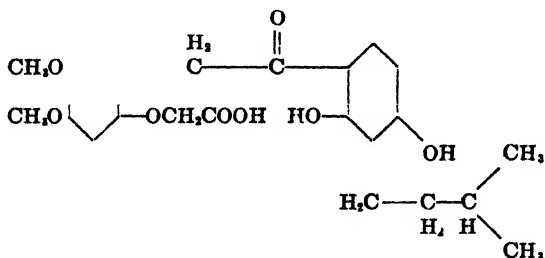
The same compound is also obtained by alkaline hydrolysis of dehydrodihydrorotenonic acid (tetrahydrodehydrorotenone) (XXXII) (31, 24), the reaction being the same as that involved in the formation of derrisic acid from dehydrorotenone.[7]

Tetrahydroderrisic acid is methylated to the methyl ester of monomethyltetrahydroderrisic acid (XXXVI) which is alkali-insoluble (24).[8]
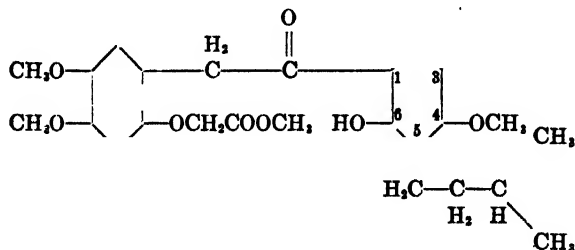
XXXVI

By the action of acetic anhydride and anhydrous sodium acetate, tetrahydroderrisic acid (XXXV) is converted by dehydration and acetylation into the monoacetyl derivative of dehydrodihydrorotenonic acid (tetrahydrodehydrorotenone) (XXXVII) (24), from which the acetyl group is easily removed.
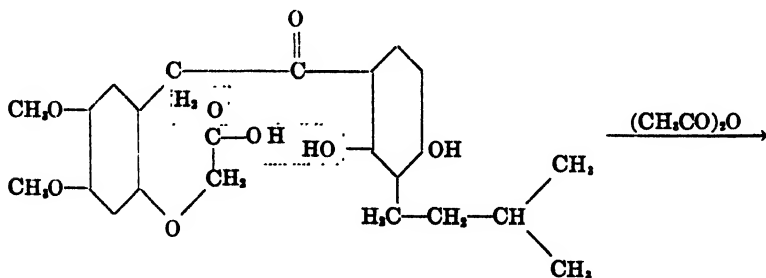
XXXV

[7] In this as well as in other instances the reductive cleavage of the oxidic linkage of the dihydrobenzofuran system can be effected either before or after some other reaction has been performed, and the same end product is obtained in each case.

[8] All rotenone derivatives which contain only one diortho-substituted phenolic group (position 6) are difficultly soluble in alkali and are not easily methylated. For example, rotenol and derritol methyl ether.
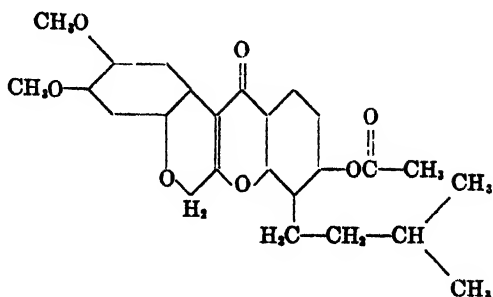
XXXVII

By the same treatment, derrisic acid (XXXIV) is converted into dehydrorotenone (XXXI), the reaction being the reverse of that involved in the conversion of dehydrorotenone into derrisic acid (24). These relations are expressed by the formulas in the following chart:

$$C_{23}H_{20}O_6 + 4H \longrightarrow \qquad C_{23}H_{24}O_6$$

Dehydrorotenone   Dehydrodihydrorotenonic acid

$$+ 2H_2O \downarrow \uparrow - 2H_2O \qquad\qquad + 2H_2O \downarrow \uparrow - 2H_2O$$

$$C_{23}H_{24}O_8 \quad + 4H \longrightarrow \qquad C_{23}H_{28}O_8$$

Derrisic   Tetrahydroderrisic acid
acid
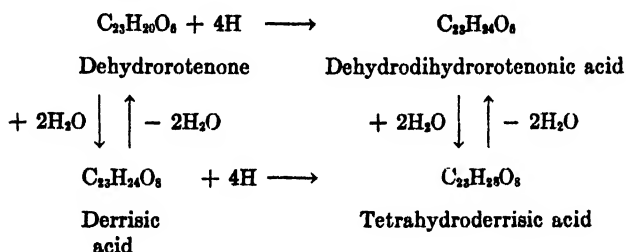
The methyl ester of methyltetrahydroderrisic acid (XXXVI) does not undergo ring closure when treated with acetic anhydride and sodium acetate but is simply converted into the 6-acetyl derivative (24). The free acid is, however, dehydrated by the same treatment, yielding 4-methyldehydrodihydrorotenonic acid (4-methyltetrahydrodehydrorotenone), which is identical with the product obtained on methylation of dehydrodihydrorotenonic acid (XXXII) (24).

The structure of derrisic acid has also been determined independently of its relation to derritol.

On oxidation of derrisic acid with hydrogen peroxide in alkaline solution, derric acid, of the formula $C_{12}H_{14}O_7$, a dibasic acid containing two methoxyl groups and one unreactive oxygen atom, is

obtained (29). Permanganate oxidation converts derric acid into its next lower homologue, risic acid, of the formula $C_{11}H_{12}O_7$ (30). Risic acid melts with evolution of gas, and on continued heating is converted with the loss of one carboxyl group into the monobasic decarboxyrisic acid of the formula $C_{10}H_{12}O_6$ (22, 47). The structure of decarboxyrisic acid has been established as XXXVIII by its synthesis from 3, 4-dimethoxyphenol, which process involved the substitution of the CH_2COOH group on the phenol hydroxyl by means of iodoacetic ester (22).

$$CH_3O-$$
$$CH_3O---OCH_2COOH$$

XXXVIII
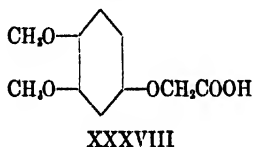
On treatment with phosphorus pentachloride, decarboxyrisic acid yields a monochloro acid of the formula $C_{10}H_{11}O_5 \cdot Cl$ (22).

The formula for risic acid has been established as XXXIX (22).

$$CH_3O \quad COOH$$
$$CH_3O \diagdown / OCH_2COOH$$

XXXIX
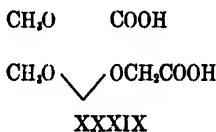
Risic acid has been synthesized from 2-hydroxy-4, 5-dimethoxy-benzoic acid (XXI) (50) by the same process as that employed for the synthesis of decarboxyrisic acid. It has also been prepared synthetically by the following steps (36).

$$CH_3O \qquad CH_3O \quad CHO \qquad CH_3O \quad CHO' \qquad CH_3O \quad COOH$$
$$CH_3O \quad OH \rightarrow CH_3O \quad OH \rightarrow CH_3O \quad OCH_2COOC_2H_5 \rightarrow CH_3O \quad OCH_2COOH$$
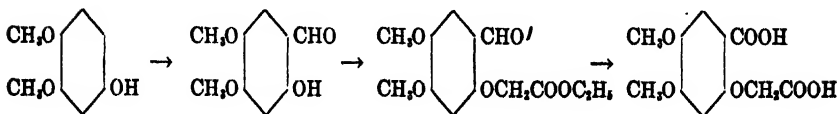
Risic acid is converted by dilute nitric acid into nitrodecarboxy-risic acid (XL) (22).

$$CH_3O \quad NO_2$$
$$CH_3O \quad OCH_2COOH$$

XL
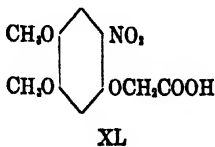
This reaction is analogous to the behavior of asaronic acid, which is converted by the same reagent into 2, 4, 5-trimethoxynitro-benzene.

$$CH_3O \text{—}\langle \text{ring} \rangle\text{—} COOH, OCH_3 + HNO_3 \rightarrow CH_3O\text{—}\langle \text{ring} \rangle\text{—}NO_2, OCH_3 + CO_2$$
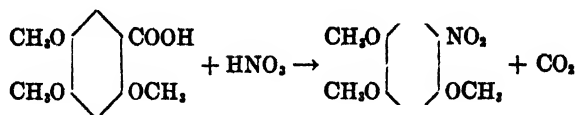
Risic acid is obtained directly from dehydrodihydrorotenonic acid (XXXII) by peroxide oxidation (31), the oxidation taking place at the double bond as well as at the carbonyl group. The formula for derric acid (XLI) can be deduced from those of its degradation products, reasoning from the fact that homoasaronic acid (XX) is obtained from derritol methyl ether (XXV) (22).

$$CH_3O\text{—}\langle \text{ring} \rangle\text{—}CH_2COOH, OCH_2COOH$$

XLI
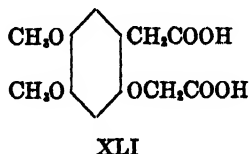
Derric acid has been synthesized through the following series of intermediary compounds (36):

$$CH_3O\text{—}\langle \text{ring} \rangle\text{—}OH \rightarrow CH_3O\text{—}\langle \text{ring} \rangle\text{—}CHO, OH \rightarrow CH_3O\text{—}\langle \text{ring} \rangle\text{—}CHO, OCH_2COOH$$

$$CH_3O\text{—}\langle \text{ring} \rangle\text{—}\left[C=C\text{—}C(O)\text{—}N=C(C_6H_5)\text{—}O\right], OCH_2COOH \rightarrow CH_3O\text{—}\langle \text{ring} \rangle\text{—}CH_2COCOOH, OCH_2COOH$$

$$CH_3O\text{—}\langle \text{ring} \rangle\text{—}CH_2COOH, OCH_2COOH$$

XLI

With the structure of derrisic acid and its relation to dehydroro-
tenone established, the nature of the groupings which compose
the skeleton of the rotenone molecule could be deduced.

REACTIONS INVOLVING THE DIHYDROBENZOPYRAN SYSTEM

Rotenone is oxidized by chromic acid (42) or by nitrous acid
(3) to rotenonone, a yellow compound of the formula $C_{23}H_{18}O_7$
(29); analogous compounds are obtained in the same manner
from iso- (50), dihydro- (29), and β-dihydro-rotenone (9), as
well as from dihydrotenonic acid (29). It is apparent that the
first step of this oxidation process consists in the formation of the
dehydro derivatives, because rotenonone and its analogues are
also obtained from the corresponding dehydro compounds (29).

Rotenonone was at first supposed to be a 1, 2-diketone formed
by the oxidation of a methylene group adjacent to a carbonyl
group (3). From the formula (XXXI) for dehydrorotenone, it is
apparent that oxidation of the methylene group in the benzopy-
ran system (B, formula I) to a carbonyl group is the only plausible
explanation for the formation of rotenonone. This change from
a benzopyran to a benzo-α-pyrone system results in the formation
of a coumarin derivative and rotenonone is, therefore, to be
represented by the formula XLII (5, 50, 23).

XLII

Rotenonone and its analogues are therefore lactones and as such
are hydrolyzed to hydroxy acids (42, 29). Rotenonone itself is
converted by the action of alkali into rotenononic acid of the

formula $C_{23}H_{20}O_8$ (29).   By energetic alkaline hydrolysis, rotenonone or rotenononic acid is further cleaved with the formation of derritol and oxalic acid (50, 5, 23).
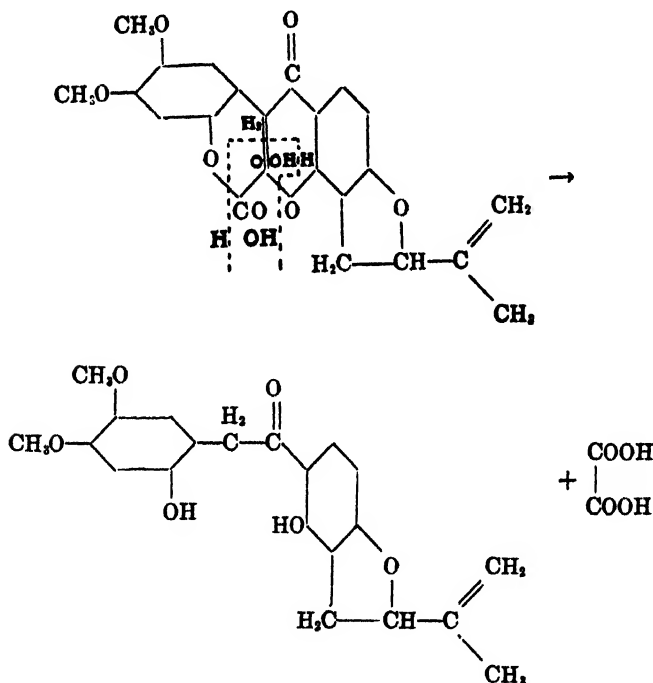
By the reverse process, rotenonone has been synthesized by the action of chloroxalyl ethyl ester on derritol (23).
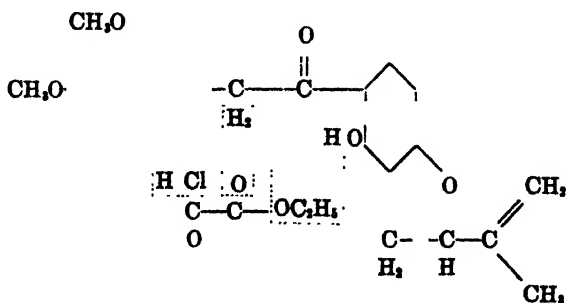
It was first supposed that rotenononic acid was the primary product resulting from simple hydrolysis of the coumarin ring present in rotenonone, to be expressed by the formula XLIII.
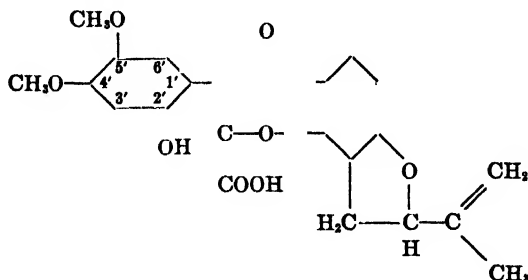
XLIII

This formula however fails to explain certain experimental facts.

By oxidation of rotenononic acid, together with tubaic acid, the dibasic abutic acid, $C_{12}H_{10}O_7$, is obtained. Abutic acid contains two methoxyl groups and an indifferent oxygen atom and is to be expressed by formula XLIV (50).
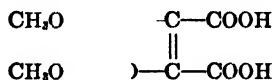
XLIV

The formation of abutic acid is accounted for by the theory of Takei (50), that the primary product of hydrolysis of rotenonone (XLII) is further hydrolyzed to the intermediary compound XLV. A new ring closure then occurs as indicated below. Formula XLVI should, therefore, be assigned to rotenononic acid (50).
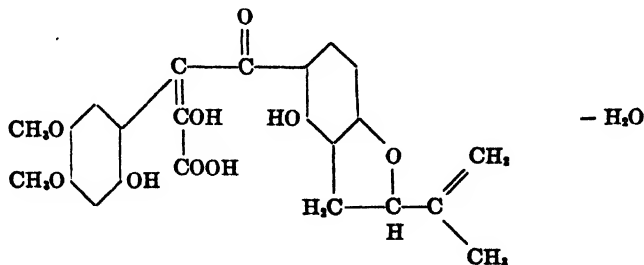
XLV
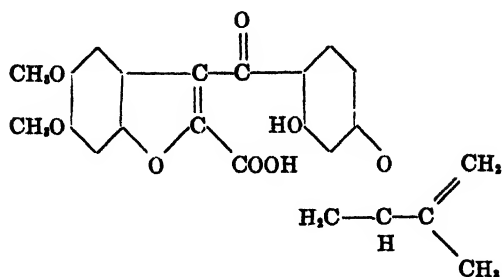
XLVI

Abutic acid (XLIV) is obtained by oxidation of XLVI.

Rotenononic acid (XLVI), in acid solution, changes over into an isomer of rotenonone, β-rotenonone, of the formula XLVII.
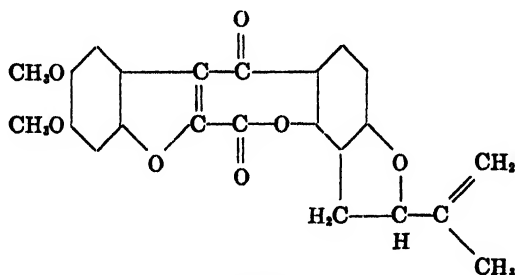
XLVII

This β-rotenonone rearranges in weak alkaline solution through the intermediary compound XLV to rotenonone (XLII) (50). Rotenononic acid is easily methylated by dimethyl sulfate or diazomethane to its methyl ether methyl ester (50, 23), which is represented by formula XLVIII.
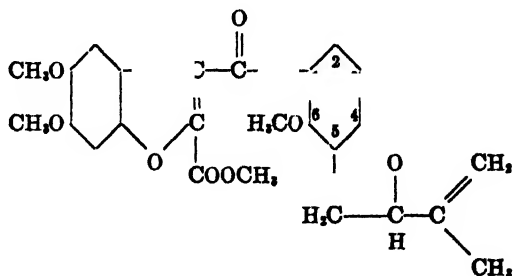
XLVIII

The corresponding acid is obtained by saponification of the ester (23). The methyl ester of methylrotenononic acid is hydrogenated to the phenolic alkali-soluble tetrahydro derivative with the opening of the oxide ring in the dihydrobenzofuran system (23).

It is remarkable that the phenolic hydroxyl group of rotenononic acid in position 6 is methylated by dimethyl sulfate, because no other derivatives, such as rotenol, derritol methyl ether, and derrisic acid, which have a free hydroxyl in this position, can be methylated by this reagent. It appears, however, that the methoxyl group in position 6 is easily saponified by alkali. The methyl ether of rotenononic acid yields derritol by energetic alkaline hydrolysis and is partly reconverted by milder alkaline treatment into rotenonone. These facts strongly support the formula XLVI proposed by Takei for rotenononic acid. On the other hand, formula XLIII for rotenononic acid is excluded, since its methyl ether, which would have a methoxyl group in position 2′, would yield by alkaline hydrolysis, derritol methyl ether (XXV), which is itself unaffected by prolonged boiling with strong alkali.

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THE BECKMANN REARRANGEMENT

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The past ten years have witnessed a considerable revival of interest on the part of organic chemists in the problems presented by the Beckmann rearrangement. Chiefly this has been due to a group of researches, initiated by Meisenheimer, which have made it necessary for organic chemists to consider seriously the advisability of reversing the configurations previously assigned by means of the Beckmann rearrangement to almost all ketoximes. These same investigations cannot but have an effect on our views of the mechanism of the Beckmann rearrangement and they should in the near future give rise to a renewed study of that mechanism. With this in mind, and particularly since the chemical literature dealing with the rearrangement is already so extensive as to make it difficult for persons not actively working on the problem to familarize themselves with it, the present survey of that literature has been prepared. For purposes of orientation we shall begin with brief descriptions of the discovery of the rearrangement, the methods employed for effecting the rearrangement, and the generality of rearrangement.

In its most general form the Beckmann rearrangement consists in the transformation of a ketoxime into an acid amide.

$$\underset{\text{NOH}}{\overset{\text{RCR}}{\|}} \rightarrow \underset{\text{O}}{\overset{\text{RCNHR}}{\|}}$$
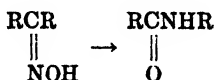
Its discovery in 1886 was quite accidental. Ernst Beckmann (1) was interested in developing a method for distinguishing between aldehydes and ketones and, in order to do so, proposed to make use of their respective oximes. It was known that aldoximes on treatment with phosphorus pentachloride furnished nitriles.

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Since a similar reaction seemed unlikely with ketoximes, Beck-
mann set out to determine the behavior of a typical ketoxime
toward this reagent, choosing benzophenone oxime for this pur-
pose. He found that the product of the reaction, after hydroly-
sis, was benzanilide and thus established the first example of the
rearrangement which still carries his name. It is of sufficient
historical interest to justify noting that three years prior to Beck-
mann's discovery, Janny (2) had found that acetoxime reacted
vigorously with phosphorus pentachloride, but he was unable to
identify the products of the reaction.

The rearrangement of a ketoxime to an acid amide can be ef-
fected by a surprisingly large number of reagents. Beckmann (1)
early showed that phosphorus pentachloride and phosphorus
oxychloride were suitable. He also employed acetyl chloride, sul-
furic acid, and especially the so-called "Beckmann's mixture,"
consisting of acetic acid and acetic anhydride saturated with
hydrogen chloride (3, 4). V. Meyer (5) shortly before this had
used acetyl chloride in special cases. More recent work by Beck-
mann (6) has shown that antimony tri- and penta-chlorides are
particularly effective, while a large number of metallic chlorides
are capable of causing rearrangement. Metallic sulfates, oxides,
and hydroxides, however, do not bring about the rearrangement.
Other workers (7, 8) have shown that hydrogen chloride and
oxime hydrochlorides will cause rearrangement, as will benzene-
sulfonyl chloride in an alkaline aqueous medium or in pyridine
(9, 10, 11). Even chloral has been found capable of rearranging
benzophenone oxime (12). Of this large list of reagents, how-
ever, only three merit more than passing mention. Sulfuric acid
is the most satisfactory reagent for cyclic oximes of the type of
cyclohexanone oxime (13). Benzenesulfonyl chloride, which is
ordinarily thought of only in connection with the Beckmann
rearrangement of the second order (see later), is of quite general
applicability and permits the carrying out of a rearrangement in
an alkaline medium. Phosphorus pentachloride, however, re-
mains the most generally applicable and the most valuable reagent.
Used in ether solution and at low temperatures it involves the
minimum of complications and is quite deservedly the reagent

which first comes to mind at mention of the Beckmann rearrangement.

The rearrangement of a ketoxime to an acid amide is a reaction of considerable generality. Not only is it undergone by most ketoximes, but it has also been observed to take place with the nitrogen alkyl ethers of aldoximes (14, 15, 16). Two cases, even, have been reported of the rearrangement of aldoximes to acid amides (17). We shall confine our attention, however, to the ketoximes. Considering the general formula of this type of substance,

$$\underset{\underset{NOH}{\|}}{RCR}$$

one may say that rearrangement will take place if the R groups are aliphatic, aromatic (18), or heterocyclic (19, 20). If aliphatic they may be of large or small molecular weight, saturated or unsaturated (21, 22). If aromatic, the presence of substituents in the R group does not in general prevent rearrangement (23). There are, of course, isolated instances of oximes which either do not rearrange or from which no definite rearrangement products have been obtained (24, 25, 26). In contrast to these individual instances there are several well-defined classes of oximes which undergo rearrangement to yield products other than acid amides. We may review these special types of rearrangements briefly.

The oximes of some cyclic ketones on rearrangement undergo ring enlargement and furnish lactams. Examples are cyclohexanone oxime (27) and fluorenone oxime (28).
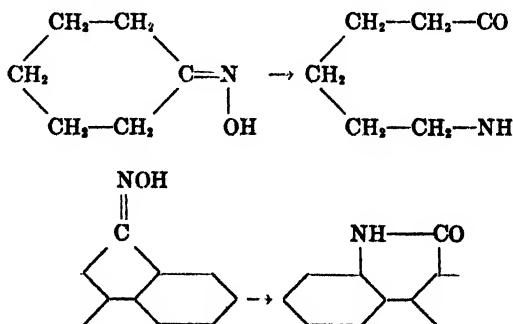
In different fashion the oximes of certain bicyclic ketones, such as camphor, yield unsaturated nitriles (29, 30),

$$
\begin{array}{cccc}
\text{CH} & & \text{CH} & \\
& & |\diagdown & \\
\diagup & & & \\
\text{CH}_2 & \text{CH}_2\text{—C—CH}_3 & \text{CH}_2 & \text{CH}_2 & \text{CH}_3\text{—}\overset{\cdot}{\text{C}}\text{—CH}_2 & \text{CH}_2 \\
| & & & | & \\
\text{CH}_2 & \text{C}\text{=}\text{NOH}^1 & \text{CH} & & \text{CN} \\
& & & & \\
& \text{C} & & \text{C} & \\
& | & & | & \\
& \text{CH}_3 & & \text{CH}_3 &
\end{array}
$$
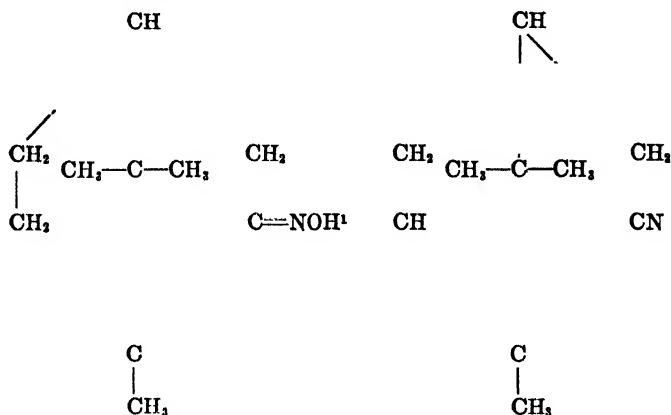
while the oximes of many unsaturated cyclic ketones furnish aromatic amines (31, 32, 33).

The oximes of α-hydroxyketones, such as benzoin, undergo cleavage on rearrangement and furnish an aldehyde and a nitrile or isonitrile (11).

$$
\begin{array}{l}
\text{C}_6\text{H}_5\text{CHOH} \\
\quad | \qquad\qquad \rightarrow \text{C}_6\text{H}_5\text{CHO} + \text{C}_6\text{H}_5\text{CN} \ (\text{C}_6\text{H}_5\text{NC}) \\
\text{C}_6\text{H}_5\text{C}\text{=}\text{NOH}
\end{array}
$$
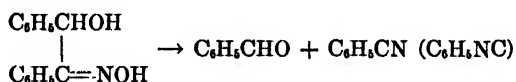
The monoximes of α-diketones, which rearrange normally on treatment with phosphorus pentachloride, undergo cleavage when treated with benzenesulfonyl chloride and alkali or pyridine (10, 34).

$$
\begin{array}{l}
\text{C}_6\text{H}_5\text{CCOC}_6\text{H}_5 \\
\quad \| \qquad\qquad \cdot \text{C}_6\text{H}_5\text{CN} + \text{C}_6\text{H}_5\text{CO}_2\text{H} \\
\text{HON}
\end{array}
$$
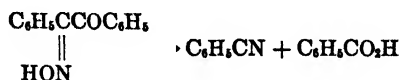
These cleavage reactions of the α-diketone monoximes and the α-hydroxyketone oximes are generally referred to as Beckmann rearrangements of the second order (10, 11).

The oximes of certain α,β-unsaturated ketones, which rearrange

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[1] Certain oximes will be formulated in this fashion for the reason that there is, at present, no satisfactory evidence for assigning a configuration to them.

normally on treatment with phosphorus pentachloride, undergo an intramolecular ring closure when treated with sulfuric acid and yield isoxazolines (35, 36, 37, 38, 39).

$$C_6H_5CH{=}CHCC_6H_5 \rightarrow C_6H_5CHCH_2CC_6H_5$$
$$\underset{HON}{\|} \qquad \underset{O{-}{-}N}{|\quad\|}$$
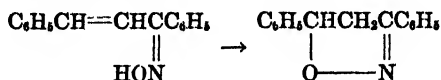
The oximes of ketones containing a benzyl group attached to the carbonyl carbon atom can be made to undergo normal rearrangement. Under certain conditions, however, they rearrange to furnish α-aminoketones or their cyclic condensation products. The mechanism of the process has been largely determined by its discoverer (40).

$$C_6H_5CH_2CCH_3 \rightarrow C_6H_5CHCOCH_3$$
$$\underset{HON}{\|} \qquad \underset{NH_2}{|}$$
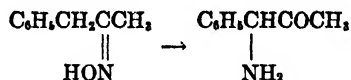
Finally attention should be called to the work of Scholl (41) on the dehydration undergone by the monoximes of certain 1-aroyl-anthraquinones.

It is perhaps advisable at this place, after having devoted one general paragraph to the normal Beckmann rearrangement and six detailed paragraphs to the consideration of special cases of abnormal rearrangements, to correct the overemphasis given of necessity to these abnormal rearrangements by this method of presentation. Accordingly attention is called to the fact that the normal rearrangement of ketoximes to acid amides far outranks all the abnormal rearrangements both in frequency of occurrence and in importance. It is with the Beckmann rearrangement in its most general form—the transformation of a ketoxime to an acid amide —-that we shall deal almost exclusively in the succeeding pages. Having outlined the methods of bringing about the rearrangement and the generality of the rearrangement, we are now in a position to consider the problems which it presents. Of these there are two major ones, distinct yet interrelated. The first deals with the configuration of ketoximes and the nature of the shift involved in their rearrangement, while the second deals with the mechanism of that shift. We shall take up these two problems in the order named, giving in each case a historical development sufficient to

make apparent the significance of the problem. From the nature of the material to be treated, our presentation falls into what will be found to be essentially two separate essays.

I. THE CONFIGURATION OF KETOXIMES AND THE NATURE OF THE SHIFT IN THE BECKMANN REARRANGEMENT

The configurations of isomeric ketoximes

With the discovery in the late eighteen-eighties that unsymmetrical ketones (reference to aldehydes is intentionally omitted) furnished in many cases two isomeric oximes, several theories were advanced to account for this isomerism. Of these theories the one which has received general acceptance is that of Hantzsch and Werner (42). According to their view, the isomerism of oximes is conditioned by three factors: the presence of two different substituents on the carbonyl carbon atom, the absence of free rotation about the carbon-nitrogen double linkage, and the distribution of the three valences of the nitrogen atom in such wise that the single valence is not in the same plane as the other two. On this view the isomerism of doubly linked trivalent nitrogen compounds is analogous to that of ethylenic compounds of the maleic–fumaric type and the isomerism of ketoximes can be represented, in a uniplanar figure, by the following formulas.

$$C_6H_5CC_6H_4OCH_3 \qquad C_6H_5CC_6H_4OCH_3$$
$$\| \qquad\qquad\qquad \|$$
$$HON \qquad\qquad\qquad NOH$$

syn Phenyl oxime   *anti* Phenyl oxime
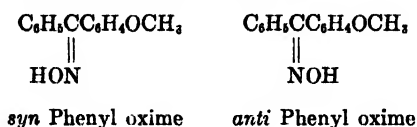
Such an explanation accounted admirably for the observed number of isomers but this, though necessary, was not sufficient. In general and in the particular case just illustrated by the formulas, that of the phenyl anisyl ketoximes, it is essential to have some method of assigning a definite formula (configuration) to each of the isomers. In 1891, a year after the general explanation of oxime isomerism had been advanced, Hantzsch (43, 44) proposed a method for determining the configurations of individual ketoximes. The method was based upon the use of the Beckmann rearrangement.

Attention was first called to the fact that isomeric ketoximes furnished, as a result of the Beckmann rearrangement, isomeric acid amides. Again using the two isomeric phenyl anisyl ketoximes as illustrations, it was known that one isomer yielded the anilide of anisic acid while the second isomer furnished the anisyl amide of benzoic acid. Hantzsch next pointed out that, regardless of the actual mechanism of the process, the rearrangement of a ketoxime could be considered, formally at least, as being essentially a shift of places between the oximino hydroxyl group and one of the groups attached to the carbonyl carbon atom, followed by ketonization of the resulting imide.

$$\begin{matrix} RCR \\ \parallel \\ NOH \end{matrix} \quad \left[\begin{matrix} RCOH \\ \parallel \\ NR \end{matrix}\right] \rightarrow \begin{matrix} RCO \\ | \\ NHR \end{matrix}$$

Hantzsch then assumed, again regardless of mechanism and purely on general stereochemical considerations, that the radical spatially nearer to the hydroxyl group would change places with the hydroxyl group—in simpler terms a *cis* shift would occur. Applied to the phenyl anisyl ketoximes we have chosen as illustrations we have:

$$\begin{matrix} C_6H_5CC_6H_4OCH_3 \\ \parallel \\ HON \end{matrix} \rightarrow \left[\begin{matrix} HOCC_6H_4OCH_3 \\ \parallel \\ C_6H_5N \end{matrix}\right] \rightarrow \begin{matrix} OCC_6H_4OCH_3 \\ | \\ C_6H_5NH \end{matrix}$$

$$\begin{matrix} C_6H_5CC_6H_4OCH_3 \\ \parallel \\ NOH \end{matrix} \rightarrow \left[\begin{matrix} C_6H_5COH \\ \parallel \\ NC_6H_4OCH_3 \end{matrix}\right] \rightarrow \begin{matrix} C_6H_5CO \\ | \\ NHC_6H_4OCH_3 \end{matrix}$$
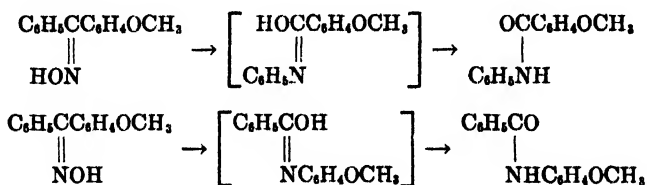
It is thus possible to assign a configuration to any ketoxime from a knowledge of its rearrangement product. For, making the assumption of a *cis* shift, the group spatially adjacent to the hydroxyl group in the oxime will appear attached to the nitrogen atom in the rearrangement product. On this basis, the *syn* phenyl configuration is assigned to the phenyl anisyl ketoxime which furnishes the anilide of anisic acid on rearrangement, while the *anti* phenyl configuration is assigned to the one which furnishes the anisyl amide of benzoic acid.

This method of assigning configurations is, it will be observed,

completely dependent upon an unverified assumption, namely, that the rearrangement involves a *cis* shift. This assumption, however, was in itself so inherently reasonable that for many years almost no objection to it was raised, while no effort was made either to verify or to disprove it. It was known that in several instances an individual ketoxime did furnish on rearrangement two isomeric amides. The difficulty in reconciling this behavior with a consistent *cis* shift was disposed of by Hantzsch (43) by showing that in general one oxime was less stable than its isomer and could easily be converted into that isomer. Doubtless, therefore, so the argument ran, the formation of both possible amides from a single oxime was due to the partial conversion of one ketoxime into its isomer before rearrangement took place. This explanation was supported by the fact that in the case of many aromatic ketoximes one isomer gave a homogeneous rearrangement product (a single acid amide) while the other isomer furnished some of that same amide but predominantly the isomeric amide. In the case of the oximes of aliphatic ketones, which so far as were examined were liquids and which quite generally gave mixtures of acid amides on rearrangement, there was not only the possibility of the interconversion of one isomer into the other, but also the further possibility that the liquid oximes were mixtures of isomers rather than chemical individuals (45).

However, as we have said, there was little or no objection to the assignment to ketoximes of configurations which were based on an examination of their rearrangement products and the assumption of a *cis* shift in the rearrangement. Indeed on this basis Hantzsch in 1892 prepared a table showing the groups commonly present in ketoximes, arranged in the order of their attraction for the oximino hydroxyl group (19). It is true that Pfeiffer (46) in 1904 and Bucherer (47) in 1914 suggested the possibility of a *trans* shift in the rearrangement, but the scant acceptance with which their suggestion was received is best illustrated by pointing out that until 1921 the configurations of all ketoximes were assigned on the basis suggested and developed by Hantzsch thirty years earlier.

In 1921 there was presented for the first time a method of deter-

mining the configuration of ketoximes which was entirely independent of the Beckmann rearrangement. In a study of triphenylisoxazole (I) Meisenheimer found that this compound furnished on ozonization the benzoate of a benzil monoxime (48). An examination of the formulas will show that this benzoate should have, if no shift in configuration has taken place after ring opening, the configuration represented by formula II.

$$C_6H_5C\text{———}CC_6H_5 \qquad C_6H_5CCOC_6H_5$$
$$\|\qquad\qquad\| \quad \rightarrow \qquad\quad \|$$
$$N\text{—}O\text{·}\text{—}CC_6H_5 \qquad\quad NOCOC_6H_5$$

$$\text{I} \qquad\qquad\qquad \text{II}$$
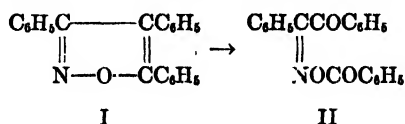
Now two benzil monoximes were known, a high melting or α-oxime and a low melting or β-oxime. Beckmann (49, 50), from an examination of the products which these two oximes furnished on rearrangement, and assuming a *cis* shift to have taken place on rearranging, had assigned to the α-oxime the configuration III and to the β-oxime the configuration IV.

$$C_6H_5CCOC_6H_5 \qquad C_6H_5CCOC_6H_5 \qquad OCCOC_6H_5$$
$$\|\qquad\qquad\qquad \| \qquad\qquad\qquad |$$
$$NOH \qquad\qquad HON \qquad\qquad C_6H_5NH$$

$$\text{III} \qquad\qquad \text{IV} \qquad\qquad \text{V}$$
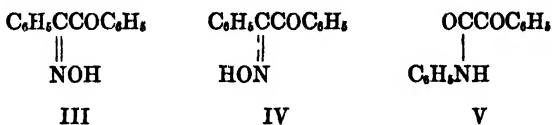
It is obvious from a comparison of formulas II and III that Meisenheimer's product from the ozonization of triphenylisoxazole should be the benzoate of the α-monoxime. Actually that product proved to be the benzoate of the β-monoxime! When it was further shown that the benzoylation of the β-oxime yielded the benzoate (II) and that the hydrolysis of this benzoate regenerated the β-oxime so that a shift of configuration was most improbable, then the full significance of Meisenheimer's work appeared. For, knowing the configuration of the β-monoxime from the ring opening to be that shown in formula III, and knowing the rearrangement product of that oxime to be the anilide of benzoylformic acid (V), it followed that the rearrangement of this oxime involved not a *cis* but a *trans* shift.

The question at once arose whether this *trans* shift in the Beck-

mann rearrangement was a general or an exceptional phenomenon. If it were general, then the Beckmann rearrangement could still be employed for assigning configurations, but almost all the configurations previously assigned would have to be reversed.   While if it were not general, then all ketoxime configurations based on the Beckmann rearrangement would be uncertain.   An answer, at least provisional, to the question of the nature and generality of the shift in the Beckmann rearrangement is possible as a result of the work done, chiefly by Meisenheimer, in the past eleven years.   Three types of attack have been made on the problem,— chemical, physical, and stereochemical.   The chemical attack, which is the one most used, has consisted in determining the configuration of an oxime by either ring opening or ring closure— assuming that rings open *cis* (51) and close *cis*.   Then, knowing the configuration of the oxime and the structure of its rearrangement product, it is possible to tell whether the rearrangement proceeds through a *cis* or a *trans* shift.   We shall review the available evidence before attempting to draw any general conclusions.

Chemical evidence of oxime configurations

The evidence of oxime configuration from ring opening is limited in amount.   In addition to the case of triphenylisoxazole already cited there are but three other examples.   The ozonization of 3,4-diphenylisoxazole-5-carboxylic acid (VI) by Kohler (20) is of particular importance, for the reaction does not furnish a derivative of a benzil monoxime, but yields directly the β-monoxime of benzil (III).

$$\underset{\text{VI}}{\overset{\displaystyle \text{C}_6\text{H}_5\text{C}\text{---}\text{---}\text{CC}_6\text{H}_5}{\underset{\text{N---O---CCO}_2\text{H}}{\overset{\parallel\qquad\parallel}{}}}} \quad \xrightarrow[\text{H}_2\text{O}]{\text{O}_3} \quad \underset{\text{III}}{\overset{\displaystyle \text{C}_6\text{H}_5\text{CCOC}_6\text{H}_5}{\underset{\text{NOH}}{\overset{\parallel}{}}}} \quad + \ (\text{CO}_2\text{H})_2$$
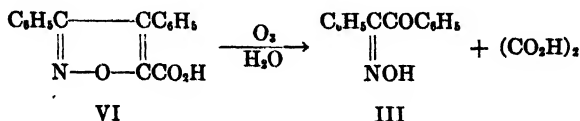
By thus confirming the configuration (III) assigned to the β-monoxime of benzil by Meisenheimer, this work strengthens the conclusion that the rearrangement of this β-monoxime involves a *trans* shift.   A final confirmation of the configuration III for the β-monoxime of benzil was afforded by the ozonization of 3,4-diphenyl-5-*p*-bromophenylisoxazole which furnished the *p*-bromo-

benzoate of β-benzil monoxime (52). The ozonization of 3,5-diphenyl-4-anisylisoxazole (VII) has also been investigated (53). This reaction furnishes the benzoate of the β-monoxime of a p-methoxybenzil (VIII). Since the oxime corresponding to this benzoate yields on rearrangement the anilide (IX), it follows that in this rearrangement also a *trans* shift has taken place.

$$C_6H_5C\text{------}CC_6H_4OCH_3 \qquad C_6H_5CCOC_6H_4OCH_3 \qquad OCCOC_6H_4OCH_3$$

$$\underset{N\text{---}O\text{---}CC_6H_5}{\| \qquad \|} \qquad \underset{NOCOC_6H_5}{\|} \qquad \underset{C_6H_5NH}{|}$$

$$\qquad\qquad VII \qquad\qquad\qquad VIII \qquad\qquad\qquad IX$$
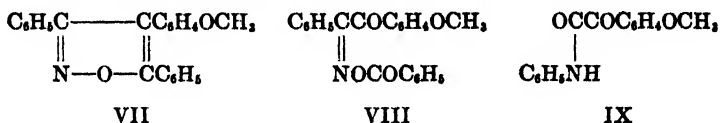
By far the greater part of our chemical evidence of oxime configurations has resulted from the study of ring closure of appropriately substituted ketoximes. As typical of this kind of evidence we may consider the results obtained with the oximes of certain ortho halogen substituted benzophenones. o-Chlorobenzophenone and o-bromobenzophenone yield each a single oxime. This single oxime in each case, as was shown in 1892 by Cathcart and V. Meyer (54), loses halogen acid on treatment with alkali to form the indoxazene (X). Strangely enough, the significance of this fact for the assignment of configurations to the oximes was not recognized at the time it was first observed. Meisenheimer (23), however, has pointed out that the loss of halogen acid by these oximes indicates the spatial proximity of the oximino hydroxyl group and the ortho substituent and is adequate evidence for assigning to the oximes the configuration XI (x = Cl, Br). Since both of the oximes in question yield on rearrangement the anilide of an ortho-halogenated benzoic acid (XII, x = Cl, Br), it follows that these rearrangements proceed through a *trans* shift.

$$\qquad\qquad O \qquad\qquad\qquad X\ HON \qquad\qquad X\ NHC_6H_5$$

$$\qquad\qquad X \qquad\qquad\qquad XI \qquad\qquad\qquad XII$$
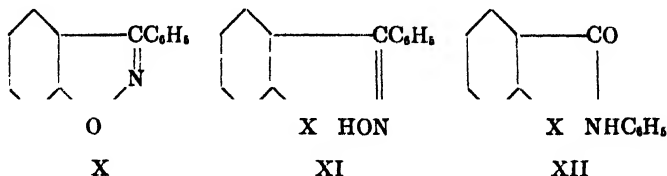
In the case of the ortho-halogenated benzophenone oximes, rather drastic treatment is necessary in order to bring about ring

closure to the indoxazene and there is the possibility of a shift in
the configuration of the oximes during this treatment.   To elim-
inate this possibility Meisenheimer took advantage of the well-
known activating effect of para placed nitro groups and examined
the oximes of 2-chloro-5-nitro-and 2-bromo-5-nitro-benzophenone
(26).   In each case but a single oxime could be obtained, and in
each case the oxime lost halogen acid very readily to form the
indoxazene (XIII).   Consequently, to the oximes was assigned
the configuration XIV (x = Cl, Br).   And since on rearrangement
each oxime yields an anilide of a substituted benzoic acid (XV,
x = Cl, Br), we are furnished with two additional examples of
trans shifts in the Beckmann rearrangement.
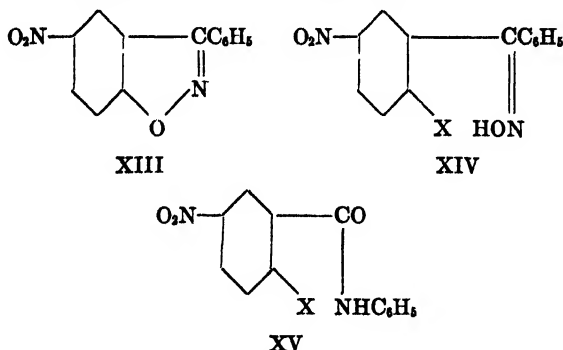
Similar studies were attempted by Meisenheimer with dinitro-
ketones of the general formula
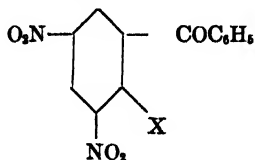
where x = Cl; Br, OCH_3, and with ketones having substituents in
both phenyl groups, but, because of experimental difficulties quite
unrelated to the question of oxime configuration, the results are
of little significance (26, 55).   Insofar as positive results were ob-
tained they indicated *trans* shifts on rearrangement of the oximes
studied.

In none of the cases so far described was it possible to isolate

both isomeric oximes. The same difficulty was experienced by Meisenheimer in studying o-hydroxybenzophenone oxime (23). The one isomer available, which yielded on rearrangement salicylanilide (XVI), could not be dehydrated to furnish the indoxazene (X). In the face of this latter fact Meisenheimer, who was by this time convinced of the generality of the *trans* shift in the Beckmann rearrangement, assigned to the oxime the configuration XVII, and attempted to account for the failure to effect a ring closure to the indoxazene by the dubious assumption that such a ring closure would, by an exercise of residual valence forces, only take place between the ortho hydroxyl group and a spatially distant (*trans*) oximino hydroxyl group. Such a spatially distant hydroxyl group would be found in the then unknown isomeric oxime (XVIII). This assumption which, as we shall see, Meisenheimer also used in other cases was shown to be unjustified when Auwers and Jordan (56) found that o, o'-dihydroxybenzophenone oxime (XIX) could not be dehydrated to yield an indoxazene, and was completely discredited when Kohler and Bruce (57) succeeded in obtaining the hitherto missing o-hydroxybenzophenone oxime and found that it, like its isomer, could not be dehydrated to furnish the indoxazene (X).
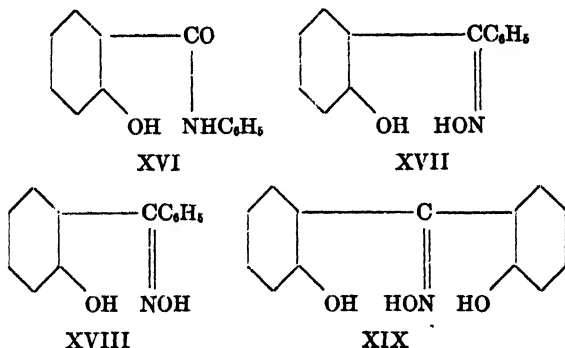
It is clear, therefore, that at present there is no method independent of the Beckmann rearrangement for establishing the configurations of the o-hydroxybenzophenone oximes and that, consequently, it is not possible to decide whether the rearrangement of these oximes proceeds through a *cis* or a *trans* shift. The same

statement applies to the various nuclear substituted o-hydroxy-benzophenone oximes (55, 56).

In contrast to these o-hydroxybenzophenone oximes it is possible with the oximes of o-aminobenzophenone (23, 58, 59) to assign configurations quite independently of the Beckmann rearrangement. Both isomers of o-aminobenzophenone oxime are known, both can be rearranged, and both can be converted into cyclic compounds. The high-melting (h) isomer on treatment with nitrous acid yields a soluble diazonium salt whose solutions on heating evolve nitrogen while the indoxazene (X) is formed. Consequently the configuration XX is assigned to the oxime. On rearrangement this oxime furnishes the anilide of anthranilic acid (XXI), obviously the result of a *trans* shift.

X   XX   XXI
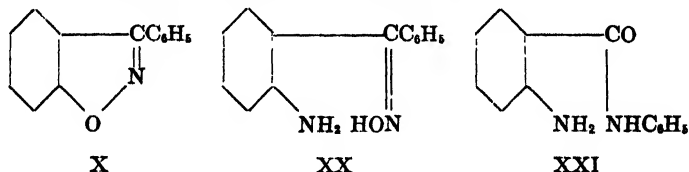
The isomeric low-melting (n) oxime on treatment with nitrous acid yields a diazo anhydride (XXIII), which in turn furnishes phenylanthranil (XXIV). (The mechanism of this process is considered later under the discussion of the oxime of o-amino-acetophenone.) On the basis of these facts the configuration XXII is assigned to the oxime. Since on rearrangement this oxime yields benzenyl phenylene amidine (XXV) we have another example of the *trans* Beckmann rearrangement.

XXIV   XXIII   XXII

XXV
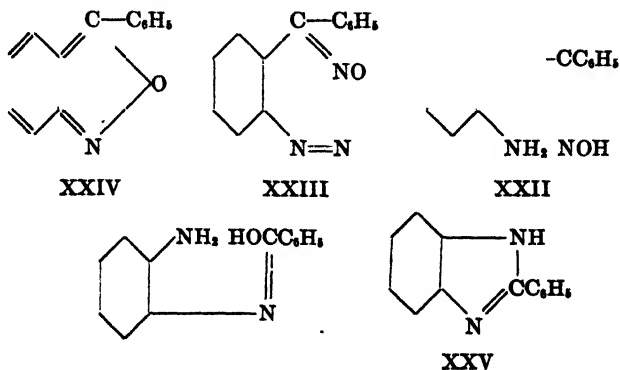
From the aminobenzophenone oximes we turn to the dioximes of benzil (48, 60). Here the facts are as definite as their interpretation is perplexing. The three benzil dioximes are known respectively as α, β, and γ. On rearrangement the α-dioxime furnishes the azoxime (XXVI), the β-dioxime furnishes oxanilide (XXVII), and the γ-dioxime furnishes benzoylphenylurea (XXVIII). For the α- and β-dioximes there is no adequate evidence independent of the Beckmann rearrangement for assigning configurations and, therefore, it is not possible to state whether their rearrangement involves a *cis* or a *trans* shift. On the older assumption of a *cis* shift the α-dioxime would be assigned the *syn* configuration and the β-dioxime the *anti* configuration. On the newer assumption of a *trans* shift these configurations would be reversed. It is true that the formation of the α-dioxime from the α-monoxime of benzil (IV) indicates the *anti* configuration for the α-dioxime and therefore a *trans* shift in the rearrangement of that dioxime. However, if the α-dioxime does have the *anti* configuration, then the formation of the azoxime (XXVI) on rearrangement involves a *trans* dehydration and ring closure. (Compare formula XXVIa. Diagram 1 gives a schematic survey of the rearrangements and ring closures observed with the benzil dioximes.)

In the case of the γ-dioxime the difficulties are even more pronounced. For to this γ-dioxime would be assigned the same, *amphi*, configuration on the basis of either a *cis* or a *trans* shift on rearrangement. Further, the formation of the γ-dioxime from the β-monoxime of benzil (III) would also indicate the *amphi* configuration. But the γ-dioxime, alone of the three benzil dioximes, can be converted into a cyclic compound—on dehydration it yields the furazane (XXIX). And the *syn* configuration which one would be tempted to assign to the γ-dioxime on the basis of this ring closure is incompatible not only with a *cis* shift on rearrangement but also, and equally so, with a *trans* shift. Meisenheimer has suggested, in order to reconcile the ring closure of the γ-dioxime with its behavior on rearrangement, that this ring closure involves a *trans* elimination of water and would be expected to take place only with an oxime having the *amphi* con-

DIAGRAM 1

The dioximes of benzil

Configurations on the basis of a *cis* shift

Configuration on the basis of a *trans* shift.

figuration. We have already seen that a similar assumption in the case of the o-hydroxybenzophenone oximes was unjustified. From what we have seen of the behavior of various o-hydroxy oximes there is good reason to suspect that the dehydration of these oximes to yield cyclic compounds is by no means the simple and direct process it appears in our ordinary formulation. It is probably better and certainly safer, since the configuration of the γ-dioxime of benzil as deduced from ring closure is consistent with neither a cis nor a trans shift on rearrangement, to admit that for the present the benzil dioximes, like the o-hydroxybenzophenone oximes, furnish no evidence one way or the other as to the nature of the shift in the Beckmann rearrangement.

In concluding the discussion of diketone oximes, attention should be called to two recent articles on this subject. Taylor (61) has discussed the configurations of the monoximes of a considerable series of α-diketones. He accepted at the outset the configurations for these oximes as deduced from their Beckmann rearrangement products with the assumption of a trans shift in the rearrangement, and then showed that the collateral evidence for configuration agreed with the configurations thus assigned. This collateral evidence is of four types: the reactivity of the carbonyl group in the oximes, the behavior of the oximes in coordinate compound formation, the solubility of the oximes, and the coupling reactions of the oximes with aromatic diazonium compounds. Meisenheimer, in a very recent investigation (62), has presented evidence for a reversal of the configurations previously assigned to certain of the oximes of camphor quinone. The configurations assigned by Meisenheimer, taken in conjunction with the behavior on rearrangement, indicate for the camphor quinone oximes studied a trans shift on rearrangement.

In addition to the oximes of purely aromatic ketones, such as benzophenone, and of α-diketones, such as benzil, considerable attention has been given to the determination of the configuration of the oximes of mixed aliphatic-aromatic ketones. This has centered largely around the o-substituted acetophenones. Many years ago Claus (63) found that the simple o-halogenated acetophenones furnished each but a single oxime and that these single

oximes did not form indoxazenes on treatment with alkali.   Meisenheimer (26) verified these observations and pointed out that the failure to form an indoxazene was indicative of the configuration XXX (x = Cl, Br), for the oximes in question.   Since, furthermore, the members of this class of oximes yield on rearrangement halogenated acetanilides (XXXI, x = Cl, Br), it follows that their rearrangement involves a *trans* shift.

XXX   XXXI
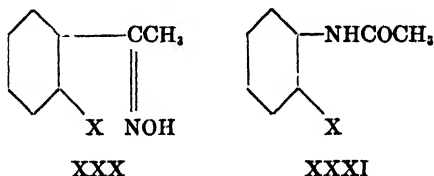
Again making use of a para nitro group to increase the reactivity of the aromatic halogen, Meisenheimer investigated 2-bromo-5-nitroacetophenone.   From this ketone he was able to obtain both isomeric oximes.   The stable oxime is not attacked by cold alkali and is only slightly attacked by hot alkali.   Consequently the *anti* phenyl configuration (XXXII) is assigned to it.   On rearrangement this oxime furnishes the 2-bromo-5-nitroanilide of acetic acid (XXXIII)—clearly the result of a *trans* shift.

XXXII   XXXIII

XXXIV   XXXV
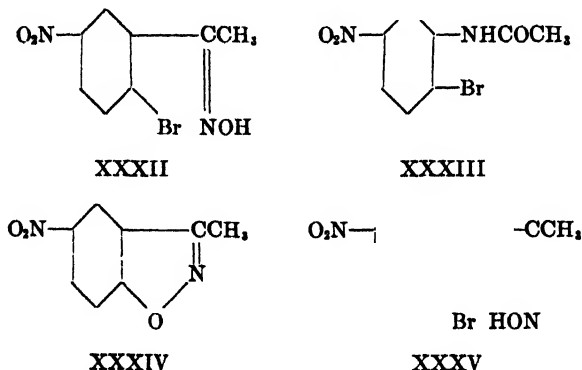
The labile oxime of this same ketone is very easily converted even by cold alkali into the indoxazene (XXXIV).   Hence to the labile oxime is assigned the *syn* phenyl configuration (XXXV). Unfortunately for the completeness of the evidence, the labile

oxime is one of the few oximes which it has not been possible to rearrange.

The one known oxime of *o*-aminoacetophenone (59) is of interest in that its behavior on diazotization has shed light on the mechanism of the formation of phenylanthranil from the low-melting oxime of *o*-aminobenzophenone. To the oxime of *o*-aminoacetophenone, on the basis of the following sequence of reactions to form methylanthranil (XXXVII), is assigned the configuration XXXVI.

XXXVI

XXXVII
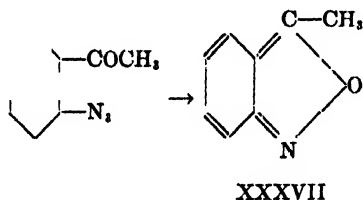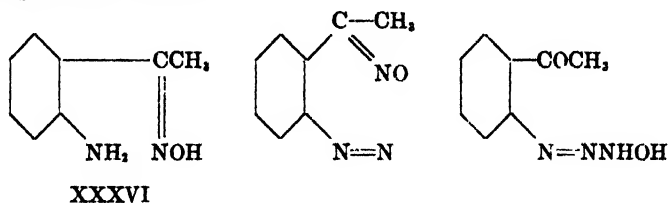
The acetophenones so far studied yield, with few exceptions, a single oxime. When it has been possible to determine the configuration of that single oxime it has been found to be the *anti* phenyl isomer. Since this isomer undergoes rearrangement in such manner that the aromatic group shifts, the rearrangement necessarily involves a *trans* shift. In the few instances where isomeric acetophenone oximes have been isolated, the statements just made apply to the stable isomer.

Only one other group of oximes, the oximes of α,β-unsaturated ketones, have had their configurations determined independently of the Beckmann rearrangement and need to be considered in discussing the nature of the shift in that rearrangement. It has long been known that α,β-unsaturated ketones, such as benzalacetophenone (XXXVIII), yield on treatment with hydroxylamine hydrochloride a single oxime, and on treatment with hydroxyl-

amine and alkali several products, among them an isoxazoline. Auwers (64, 35) has assigned a configuration to the oxime of benzalacetophenone on the following grounds. First, because the formation of the isoxazoline (XL) proceeds, according to Auwers' views, through the oxime (XXXIX) as an intermediary, there remains only the configuration XLI for the one oxime actually isolated. Second, because benzalacetophenone oxime is not converted into a cyclic compound by alkali, while α-bromobenzalacetophenone oxime, to which Auwers assigns the configuration XLII, is cyclicized by this reagent, the configuration XLI is again assigned to benzalacetophenone oxime. With this configuration assigned to the oxime it follows, since on rearrangement the oxime yields cinnamanilide (XLIII), that the rearrangement proceeds through a *cis* shift.

$$C_6H_5CH{=}CHCOC_6H_5 \qquad \underset{\underset{HON}{\|}}{C_6H_5CH{=}CHCC_6H_5} \qquad \underset{\underset{O\text{——}N}{|\qquad\|}}{C_6H_5CHCH_2CC_6H_5}$$

XXXVIII   XXXIX   XL

$$\underset{\underset{NOH}{\|}}{C_6H_5CH{=}CHCC_6H_5} \qquad \underset{\underset{HON}{\|}}{C_6H_5CH{=}CBrCC_6H_5} \qquad C_6H_5CH{=}CHCONHC_6H_5$$

XLI   XLII   XLIII
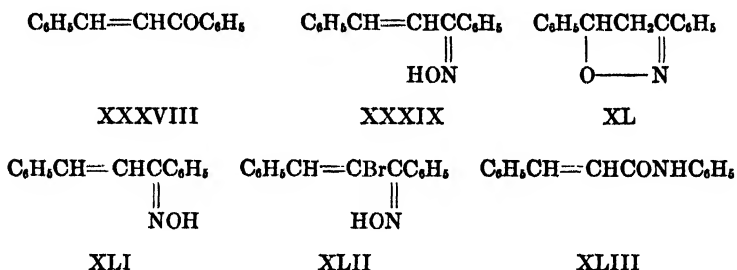
The conclusions of Auwers have not gone unchallenged by other workers (38, 39). In the case of benzal-p-bromoacetophenone (XLIV) it has been possible to isolate not only the isoxazoline (XLV) but also both of the isomeric oximes and to show that neither oxime yields the isoxazoline on treatment with alkali. The configuration of the predominant oxime, which corresponds to the one oxime obtained from benzalacetophenone, was established as shown in formula XLVI, by bromination to yield the dibromo oxime (XLVII) and by the conversion of this dibromo oxime into the isoxazole (XLVIII). It was also possible to show, by going back from the dibromo oxime to the unsaturated oxime, that no shift in configuration had taken place on bromination. With the configuration XLVI established for the oxime which on rearrangement furnishes the p-bromoanilide of cinnamic acid

(XLIX), this rearrangement must involve a *trans* shift. The configuration of the second oxime of benzal-*p*-bromoacetophenone could not be established by ring closure but had to be assigned by exclusion, for it was found that this oxime (L) on bromination underwent a shift of configuration and furnished the dibromo oxime (XLVII). From this work it would follow that the rearrangement of these α,β-unsaturated oximes proceeds through a *trans* shift. In two recent publications Auwers (36, 37) has shown from a study of the oximes of dibenzalacetone that his previous argument that an oxime with its hydroxyl group spatially adjacent to an ethylenic double bond would be unstable and would isomerize to an isoxazoline is not valid. Further, from an as yet incomplete comparison of the oximes of benzalacetophenone and benzalacetone and their derivatives, he has concluded that while the configuration he formerly advanced for benzalacetophenone oxime can no longer be considered as proved, still the alternative configuration derived from the work with benzal-*p*-bromoacetophenone oxime likewise cannot be considered to be conclusively established. Although there is not as yet complete agreement between the various workers on the question of the configurations of the oximes of α,β-unsaturated ketones, it would seem that the configurations established in the case where both isomeric oximes were isolated are the more reliable and that, therefore, it is legitimate to conclude that the rearrangement of α,β-unsaturated ketoximes involves a *trans* shift.

$$C_6H_5CH\!\!=\!\!CHCOC_6H_4Br \qquad \underset{\underset{O\text{----}N}{|\quad\quad\|}}{C_6H_5CHCH_2CC_6H_4Br}$$

XLIV   XLV

$$\underset{\underset{HON}{\|}}{C_6H_5CH\!\!=\!\!CHCC_6H_4Br} \qquad \underset{\underset{HON}{\|}}{C_6H_5CHBrCHBrCC_6H_4Br}$$

XLVI   XLVII

$$\underset{\underset{O\text{----}N}{|\quad\|}}{C_6H_5C\!\!=\!\!CHCC_6H_4Br} \qquad C_6H_5CH\!\!=\!\!CHCONHC_6H_4Br \qquad \underset{\underset{NOH}{\|}}{C_6H_5CH\!\!=\!\!CHCC_6H_4Br}$$

XVIII   XLIX   L
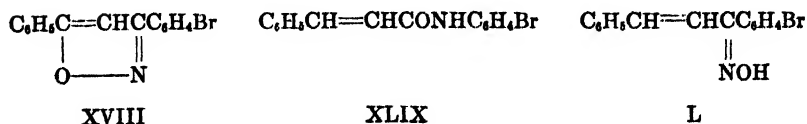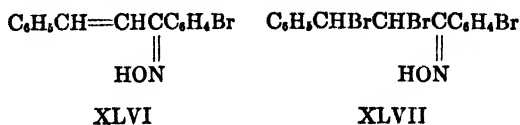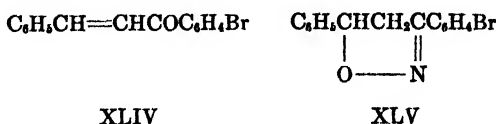
Physical evidence of oxime configurations

This completes our survey of the chemical evidence for oxime configurations and we may now consider the physical evidence on this point which has been accumulated in the last few years. This evidence in the main deals with the solubility of oximes (65), and their behavior in salt and coördinate compound formation (61, 66). In general, the evidence is favorable to oxime configurations which, taken in conjunction with the rearrangement products of the oximes in question, indicate *trans* shifts on rearrangement (67). Perhaps the most interesting single piece of physical evidence available at present is the measurement by Sutton and Taylor (68) of the dipole moments of the nitrogen methyl ethers of the oximes of *p*-nitrobenzophenone. The ether obtained from the α-oxime possesses a dipole moment slightly more than six times as large as the ether obtained from the β-oxime. Hence to the former ether is assigned the configuration LI and to the latter ether the configuration LII. On the assumption that no shifts have occurred on alkylation the α-oxime is assigned formula LIII and the β-oxime formula LIV. Since the α-oxime on rearrangement furnishes the anilide of *p*-nitrobenzoic acid (LV), while the β-oxime furnishes the *p*-nitroanilide of benzoic acid (LVI), the rearrangement of these oximes involves *trans* shifts.

O₂N—⟨ ⟩—C—⟨ ⟩   O₂N—⟨ ⟩—C—⟨ ⟩
               ‖   ‖
            ONCH₃   CH₃NO

           LI   LII

O₂N—⟨ ⟩—C—⟨ ⟩   O₂N—⟨ ⟩—C—⟨ ⟩
               ‖   ‖
             HON   NOH

          LIII   LIV

O₂N—⟨ ⟩—CONHC₆H₅   O₂N—⟨ ⟩—NHCOC₆H₅
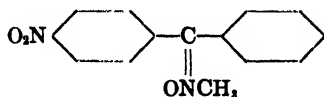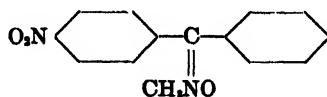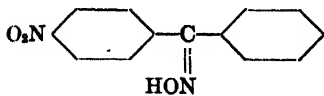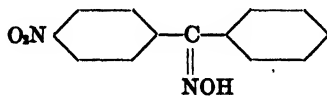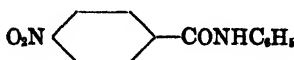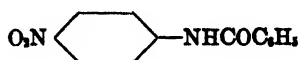
           LV   LVI

Stereochemical evidence of oxime configuration

Finally, there is the stereochemical evidence of oxime configuration to be considered. Meisenheimer, basing his attack on the recent work which has shown that hindrance to free rotation gives rise in many cases to isomerism (69), has studied the oximes of 1-aceto-2-hydroxy-3-naphthoic acid (70). This substance would be expected to furnish two oximes. One of these, the *syn* methyl (LVII), should not be resolvable, while the other, the *anti* methyl (LVIII) should, because of the hindrance to rotation about the nitrogen-oxygen linkage, be obtained as a racemic form capable of being resolved into its active components. These predictions were verified by experiment. The oxime which is not resolvable, the *syn* methyl isomer (LVII), was rearranged—to avoid complications the ethyl ester rather than the free acid was taken for rearrangement—and furnished the substituted naphthyl amide of acetic acid (LIX). The oxime which is resolvable, the *anti* methyl isomer (LVIII), on rearrangement, again *via* the ethyl ester, furnished the methyl amide of a substituted naphthoic acid (LX). In both cases, the first ones where oxime configurations have been determined on stereochemical rather than chemical grounds, the configurations so determined, taken in conjunction with the rearrangement products of the oximes, indicate unequivocally *trans* shifts on rearrangement.
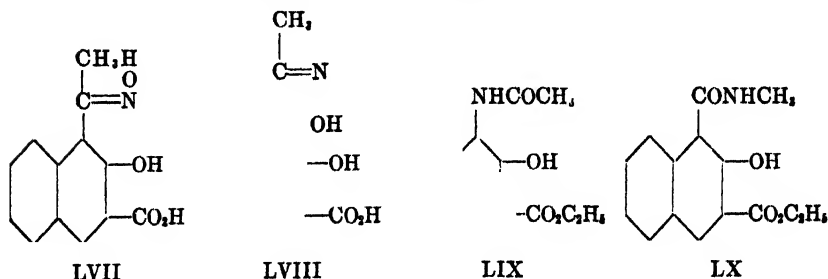
LVII   LVIII   LIX   LX

The generality of the trans shift in the Beckmann rearrangement

This concludes our survey of the evidence dealing with the nature and generality of the shift in the Beckmann rearrangement of ketoximes. What conclusions may be drawn from that evi-

dence? At the outset it may be said that, with one exception, in every case where it has been possible to establish the configuration of a ketoxime by chemical, physical, or stereochemical means the configuration so established, taken in conjunction with the rearrangement product of the oxime, indicates that a *trans* shift has taken place on rearrangement. The one exception is the γ-dioxime of benzil whose configuration as deduced from ring closure was, it will be remembered, incompatible not only with a *trans* shift but also with a *cis* shift. Once granted that in all established cases the rearrangement involves a *trans* shift, the question arises whether we are justified in assuming that the Beckmann rearrangement invariably proceeds through a *trans* shift. Such an assumption obviously involves a considerable amount of what may be termed logical extrapolation, but it has in its favor that it is the simplest explanation which fits the known facts. In view of the amount, the variety, and the consistency of the evidence favoring a *trans* shift, it is the writer's opinion that we are justified in assuming that the *trans* shift is general, and we may safely derive the configuration of ketoximes from a study of their rearrangement products and the assumption of a *trans* shift on rearrangement.[2,3] It is only fair to point out, however, that any answer other than a statistical one to the question of the generality of the *trans* shift is not yet possible and will not become possible by the simple numerical process of collecting additional examples of *trans* shifts. The collection of such additional examples will of course increase the probability that our assumption of a

[2] Raikowa (71) has questioned the validity of the use of the Beckmann rearrangement for determining the configuration of any ketoxime having a hydrogen atom on a carbon atom alpha to the C=N group because of the possible existence of iso-oximes. The none too substantial evidence adduced in favor of this view has been examined critically by Auwers (72), who was unable to verify the facts cited by Raikowa. Compare also reference 104.

[3] We have avoided up to this point the consideration of the configuration of aldoximes. However, attention should be called to the work of Brady and Bishop (73) which indicates that aldoxime configurations will probably require the same revision now being given to the configurations of ketoximes. Also to the fact that the Beckmann rearrangement of the second order must, in view of the revised configurations assigned to the benzil monoximes, be considered as involving a *trans* cleavage.

general *trans* shift is correct, and these examples will be particularly valuable when they deal with classes of oximes as yet unstudied from this point of view, but a final answer to the question of the nature and generality of the shift will be possible only when the forces which bring about the Beckmann rearrangement and the mechanism of the rearrangement are known.

At this point a digression is necessary in order to make clear that the question whether the shift in the Beckmann rearrangement is *cis* or *trans* does not enter into consideration when the rearrangement is used for the purpose of determining the structure of ketoximes and thereby the structure of the ketones from which the oximes are derived.   This is of importance, since the Beckmann rearrangement, followed by hydrolysis and identification of the resulting acid and amine, is an extremely valuable method of determining the structures of oximes and their parent ketones. An example will make clear our point.   From any given oxime (LXI) one would obtain by a *trans* shift the amide (LXII), by a *cis* shift the isomeric amide (LXIII).   The isomeric oxime (LXIV) by a *trans* shift would furnish the amide (LXIII), by a *cis* shift the amide (LXII).   But from both oximes only two amides can result.   And from either amide one can deduce the *structure* (not the configuration) of the oxime as LXV and hence the *structure* of the parent ketone as LXVI.

$$RCR_1$$
$$\|$$
$$NOH$$

trans   LXI   *cis*

$$OCR_1$$
$$|$$
$$RNH$$

LXII   *cis*

$$RCO$$
$$|$$
$$NHR_1$$

trans   LXIII

$$RCR_1$$
$$\|$$
$$HON$$

LXIV

$$R{>}C{=}NOH$$
$$R_1$$

LXV

$$R{>}C{=}O$$
$$R_1$$

LXVI
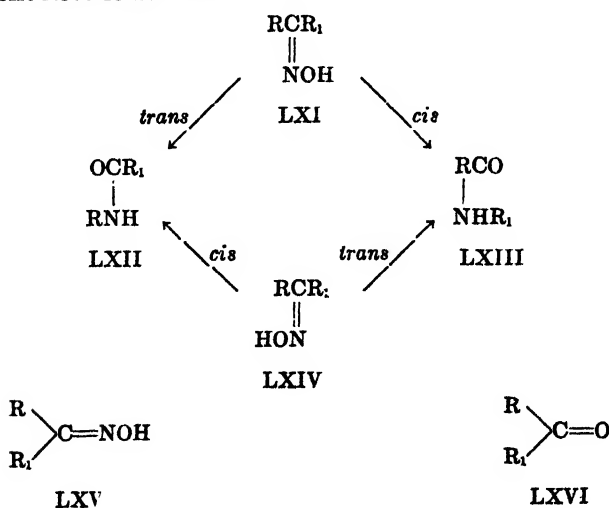
The question whether the shift on rearrangement of a ketoxime is *cis* or *trans* is, we may repeat, of fundamental significance in connection with the configuration of ketoximes and the mechanism of the Beckmann rearrangement, but it has no bearing on the use of the rearrangement for the determination of structure.

We may now proceed to an examination of the various mechanisms proposed to elucidate the Beckmann rearrangement, keeping particularly in mind as a result of the discussion to this stage that any mechanism to be satisfactory must take into account the occurrence of the *trans* shift on rearrangement.

II. THE MECHANISM OF THE BECKMANN REARRANGEMENT

The views of Beckmann concerning the mechanism of the rearrangement

It is only appropriate that we begin our review of the work on the mechanism of the Beckmann rearrangement with a consideration of the views of Beckmann himself. Particularly is this true since, as we shall see, most of the chemists who have devoted their efforts to a study of this problem have come at the end of their work, whatever they may have thought at the beginning, to views essentially the same as those of Beckmann. Fairly early in his study of the rearrangement, Beckmann (74) came to the conclusion that because of the wide variety of reagents capable of effecting the rearrangement of ketoximes it was highly improbable that any single intermediate compound or even any single type of intermediate compound was involved. In his opinion the rearrangement was best represented in the following formal fashion

$$\begin{matrix} \text{RCR} \\ \| \\ \text{NOH} \end{matrix} \rightarrow \begin{bmatrix} \text{RCOH} \\ \| \\ \text{NR} \end{bmatrix} \rightarrow \begin{matrix} \text{RCO} \\ \| \\ \text{NHR} \end{matrix}$$

and it consisted of the migration of the hydroxyl group and one of the hydrocarbon residues of the oxime. The function of the reagent employed was purely and simply that of a catalyst. Beckmann (18), after the appearance of the work of Meisenheimer on

the *trans* shift, accepted the existence of such a shift and, while retaining his fundamental idea of a direct interchange of groups, employed the concept of partial valences to account for the fact that the groups spatially distant changed places. (The use of partial valences in explaining the *trans* shift will be considered in detail later.)

The mechanism suggested by Wallach

Beckmann's view of the direct interchange of groups was, of course, anathema to most organic chemists, as it still is in fact to many. Perhaps the reason for this unwillingness to accept the idea of a simple shift of groups, which is found not only in connection with the Beckmann rearrangement but also in connection with other rearrangements, lies in the thought that such an admission involves a weakening, if not an actual denial, of the validity of structural formulas. At any rate an attempt was not lacking to account for the Beckmann rearrangement on the basis of conventional intermediate compounds of such nature as to permit the establishment of the new linkages before the old ones were broken. The suggestion of Wallach may be considered in this connection. Wallach (75) assumed in the rearrangement of aliphatic and of mixed aliphatic-aromatic ketoximes the formation of a three-membered heterocyclic intermediate. According to this view the following steps were involved in the rearrangement.

$$CH_3CCH_3 \quad CH_3C{-}CH_3 \quad CH_3COH \quad CH_3CO$$
$$\underset{NOH}{\|} \;\rightarrow\; \underset{N}{\|}{\diagup} \;\rightarrow\; \underset{NCH_3}{\|} \;\rightarrow\; \underset{NHCH_3}{|}$$
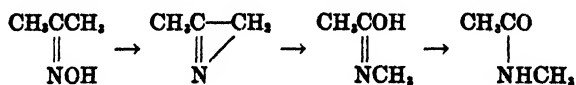
Montagne (76) almost immediately pointed out that this ingenious mechanism could be tested experimentally in the case of aromatic ketoximes and described the results of such a test. It will be observed from the reaction series A that the rearrangement of *p, p'*-dichlorobenzophenone oxime according to Wallach's view should yield the *m*-chloroanilide of *p*-chlorobenzoic acid—that is, after rearrangement the group which has migrated must be attached to the nitrogen atom by a different carbon atom than that

by which it was attached to the carbonyl carbon atom in the oxime.[4]
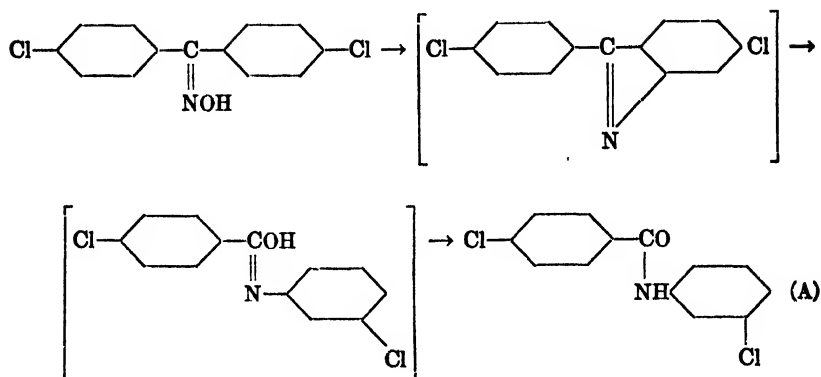
When Montagne rearranged the oxime of p,p'-dichlorobenzophenone he found that the product was not the m-chloroanilide of p-chlorobenzoic acid but was the p-chloranilide of that acid—that is, after rearrangement the group which has migrated is attached to nitrogen by the same carbon atom by which it was attached to the carbonyl carbon atom in the oxime. This, of course, disposed of Wallach's mechanism so effectively that it is almost superfluous to point out that it would be extremely difficult, if not impossible, to account for a *trans* shift on the basis of that mechanism.

Sluiter's measurements of the rate of rearrangement

Measurements of the rate of rearrangement of acetophenone oxime were made by Sluiter (77), who used concentrated sulfuric acid as both solvent and reagent and who followed the progress of the reaction by hydrolysis of the resulting acetanilide and titration of the acetic acid thus liberated. Sluiter found that the reac-

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[4] The argument still holds even if one cares to make the very unlikely assumption that the intermediate anhydro compound is formed through the *meta* position in the phenyl group.
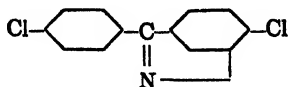
tion had a large temperature coefficient and that the reaction velocity was increased by an increase in the strength of the sulfuric acid used. He found, further, that with acid of a given strength and at a given temperature the reaction measured was of the first order, for the amount of acetanilide formed under these conditions was proportional only to the amount of oxime present. On the basis of this last fact Sluiter formulated the rearrangement in the manner shown in the reaction series B.

$$\underset{\substack{\| \\ NOH}}{RCR'} + HX \xrightarrow{\text{rapid}} \underset{\substack{\| \\ NX}}{RCR'} \xrightarrow{\text{slow}} \underset{\substack{\| \\ NR'}}{RCX} + H_2O \xrightarrow{\text{rapid}} \underset{\substack{| \\ NHR'}}{RCO} \quad (B)$$
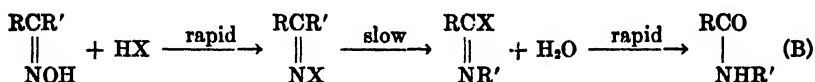
Sluiter's interpretation of his results offers an illustration of the caution which must be exercised in analyzing organic reactions solely on the basis of physical measurements. His results, as well as later experiments by Kuhara, do show definitely that the slowest reaction involved in the Beckmann rearrangement is a reaction of the first order; they give, however, no evidence of the nature of that first order reaction and certainly cannot be considered as proof that any particular first order reaction is the one actually measured. Indeed later, as we shall see shortly, Stieglitz showed that intermediates of the type postulated by Sluiter did not undergo the Beckmann rearrangement.

Stieglitz' study of the Beckmann rearrangement

Next to be considered are the efforts of Stieglitz and his collaborators to determine the mechanism of the Beckmann rearrangement. Stieglitz' work, covering the period from 1896 to 1916, is with that of Kuhara, which we shall consider later, the most important work on this problem. Stieglitz (78), like Hoogewerff and van Dorp (79) before him, called attention to the analogy between the Beckmann rearrangement of oximes and the Hofmann degradation of amides—in each case a group attached to carbon in the starting material is found attached to nitrogen in the end product of the rearrangement. He further suggested that in each case the rearrangement might proceed through a substance

containing a univalent nitrogen atom as an intermediary. Thus in the case of the Hofmann reaction,

$$\text{RCONH}_2 \rightarrow \text{RCONHBr} \rightarrow \text{R—}\underset{\underset{O}{\|}}{\text{C}}\text{—N} \rightarrow \text{R—N}{=}\text{C}{=}\text{O}$$
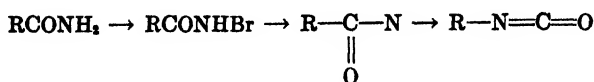
and in the case of the Beckmann rearrangement,

$$\underset{R}{\overset{R}{>}}\text{C}{=}\text{NOH} \rightarrow \underset{R}{\overset{R}{>}}\overset{\overset{Cl}{|}}{\text{C}}\text{—N}\underset{\backslash H}{\overset{/OH}{<}} \rightarrow \underset{R}{\overset{R}{>}}\overset{\overset{Cl}{|}}{\text{C}}\text{—N} \rightarrow \overset{\overset{R}{\backslash}\overset{Cl}{|}}{\text{C}}{=}\text{NR} \rightarrow \text{RCONHR}$$
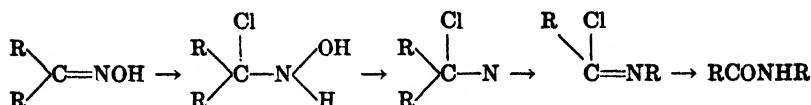
This hypothesis was in accord with the observed facts that to bring about the Hofmann rearrangement alkali was used as the reagent, while for the Beckmann rearrangement an acidic and dehydrating reagent was used. It was not in accord with the view held by many chemists (80) that the first step in the Beckmann rearrangement was the replacement of the oximino hydroxyl group by a "negative" group to yield an intermediate product such as I. Stieglitz was then able to show that a substance similar to I, namely the chloroimino ester II, did not undergo a rearrangement of the Beckmann type (78). In later work isomeric chloroimino esters (81), corresponding to isomeric ketoximes, were obtained and neither isomer could be rearranged while, finally, it was possible to isolate isomeric chloroimino ketones (III and IV) themselves and to show that even they underwent no Beckmann rearrangement (82, 83).

$\underset{\underset{\text{NCl}}{\|}}{\text{RCR}}$	$\underset{\underset{\text{NCl}}{\|}}{\text{C}_6\text{H}_5\text{COC}_2\text{H}_5}$	$\underset{\underset{\text{NCl}}{\|}}{\text{C}_6\text{H}_5\text{CC}_6\text{H}_4\text{Cl}}$	$\underset{\underset{\text{ClN}}{\|}}{\text{C}_6\text{H}_5\text{CC}_6\text{H}_4\text{Cl}}$
I	II	III	IV
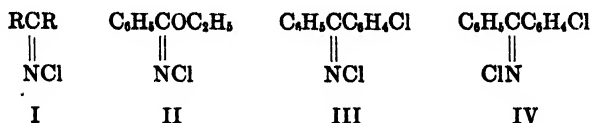
Meanwhile the Curtius rearrangement of acyl azides, like the Hofmann degradation of amides, was shown to be capable of assimilation by the univalent nitrogen hypothesis (84), while Jones (85) pointed out that the Lossen rearrangement of hydrox-

amino acids could be similarly treated. We have then a formal analogy for these four types of carbon-nitrogen rearrangements.

Hofmann: $R—\underset{\underset{O}{\|}}{C}—NHBr \rightarrow R—\underset{\underset{O}{\|}}{C}—N \rightarrow R—N{=}C{=}O$ (C)

Curtius: $R—\underset{\underset{O}{\|}}{C}—N{\overset{\overset{N}{\diagup}}{\underset{N}{\diagdown}}\|} \rightarrow R—\underset{\underset{O}{\|}}{C}—N \rightarrow R—N{=}C{=}O$ (D)

Lossen: $R—\underset{\underset{O}{\|}}{C}—NHOH \rightarrow R—\underset{\underset{O}{\|}}{C}—N \rightarrow R—N{=}C{=}O$ (E)

Beckmann: $R—\underset{\underset{R}{|}}{C}{=}NOH \rightarrow R—\underset{\underset{R}{|}}{\overset{\overset{Cl}{|}}{C}}—NHOH \rightarrow R—\underset{\underset{R}{|}}{\overset{\overset{Cl}{|}}{C}}—N \rightarrow R—\overset{\overset{Cl}{|}}{C}{=}NR$ (F)

                                 V   VI
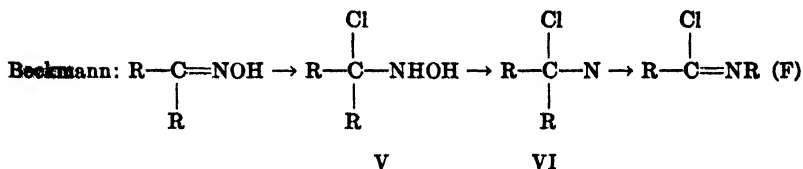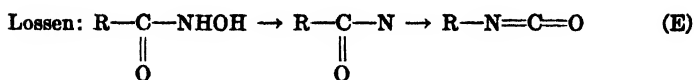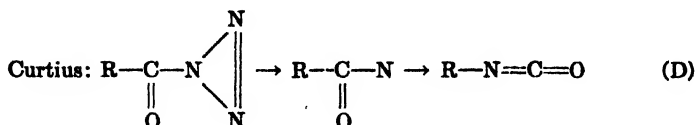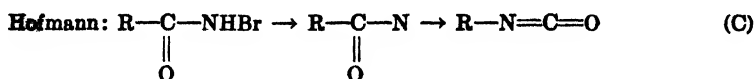
In all of these reactions, according to Stieglitz, the reagent gives rise to the univalent nitrogen derivative and then the tendency of the univalent nitrogen atom to revert to a more normal valence state is the driving force which brings about the rearrangement.

From a comparison of the reaction series C, D, E, and F, it will be observed that the application of the univalent nitrogen theory to the Beckmann rearrangement involves, in contrast to its application to the other rearrangements, a preliminary addition reaction in order to furnish a product (V) which in turn is capable of forming the univalent nitrogen derivative (VI). No such addition product as V has ever been isolated, but Stieglitz (86, 87) obtained evidence, by analogy, for the behavior of such a substance from a study of triphenylmethylhydroxylamine (VII). This latter substance, like the intermediate V, is a methylhydroxylamine with three substituents on the methyl carbon atom. When it is treated with certain of the reagents which bring about the Beckmann rearrangement, triphenylmethylhydroxylamine does

undergo a carbon-nitrogen rearrangement to furnish benzophenone anil (VIII).

$$(C_6H_5)_2CNHOH \rightarrow (C_6H_5)_2C{=}NC_6H_5$$
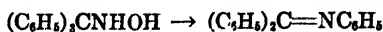
$$\text{VII} \qquad\qquad \text{VIII}$$

While the development which we have just sketched was taking place, Montagne (88) brought forward a critical analysis of the univalent nitrogen theory which completely undermined the validity of that theory, as it was then stated, insofar as the Beckmann rearrangement was concerned. Montagne called attention to the fact that the addition products corresponding to V would be identical from stereoisomeric ketoximes. For, as will be seen from formulas IX and X, the addition of halogen acid to the carbon-nitrogen double bond results in the formation of a single linkage, and with free rotation possible about this carbon-nitrogen single linkage the differences between IX and X disappear. Consequently, since the addition products from stereoisomeric ketoximes are identical, it follows that the same univalent nitrogen intermediate would be formed from both isomeric oximes, and both oximes should yield the same amide as their rearrangement product. Of course, stereoisomeric oximes on rearrangement yield not the same but isomeric amides, so that the univalent nitrogen theory in the form in which it was first advanced is untenable.

$$
\begin{array}{ccc}
\text{RCR}' & & \text{RCR}' \\
\| & & \| \\
\text{NOH} & & \text{HON} \\
\\
\downarrow & & \downarrow \\
\\
\text{Cl} & & \text{Cl} \\
| & & | \\
\text{R}{-}\text{C}{-}\text{R}' & \longleftarrow & \text{R}{-}\text{C}{-}\text{R}' \\
| & & | \\
\text{HNOH} & & \text{HONH} \\
\\
\text{IX} & & \text{X}
\end{array}
$$

Stieglitz was quick to admit the validity and importance of Montagne's criticism and to modify the univalent nitrogen theory, insofar as ketoximes were concerned, accordingly. The modified

theory was formulated in electronic terms at a time when a non-polar linkage was assumed to be due to the complete transfer of an electron from one atom to another. The reader is therefore referred to the original article (87) for the details of this electronic formulation, as we shall present the modified theory in more modern terms as, indeed, has already been done elsewhere with Stieglitz' approval (89). In its essentials the new view involved the addition of hydrogen chloride to the nitrogen atom of the oxime to yield an ammonium salt (XI).

This ammonium salt, under the influence of the dehydrating agent used to bring about the rearrangement, loses a molecule of water to form the salt (XII) which is considered to be essentially a univalent nitrogen derivative. By this scheme the necessity for breaking the carbon-nitrogen double linkage on the oxime is avoided, but it is difficult to see any significance or reality in the hypothetical salts such as XII.

$$\begin{array}{ccccccc}
\underset{\text{XI}}{\begin{matrix}RCR'\\ \parallel \\ NOH\end{matrix}} & \rightarrow & \underset{\text{XII}}{\left[\begin{matrix}RCR'\\ \parallel \\ HNOH\end{matrix}\right]^{+}Cl'} & - & \left[\begin{matrix}RCR'\\ \parallel \\ N\end{matrix}\right]^{+}Cl' & \rightarrow & \left[\begin{matrix}RC\\ \parallel\parallel\parallel \\ NR'\end{matrix}\right]^{+}Cl' & \rightarrow & \begin{matrix}RCCl\\ \parallel \\ NR'\end{matrix} & \text{(G)}
\end{array}$$

In the meantime Stieglitz (87, 90) had been continuing the study of the triphenylmethylhydroxylamines and had found that methyl triphenylmethylhydroxylamine (XIII), which would not be expected to furnish a univalent nitrogen derivative, does undergo a rearrangement involving the shift of a phenyl group from carbon to nitrogen.

$$(C_6H_5)_3CN\begin{matrix}\diagup CH_3\\ \diagdown OH\end{matrix} \rightarrow (C_6H_5)_2CO + C_6H_5NHCH_3$$

XIII

As a result of this work and of the work of Kuhara, Stieglitz concluded that the Beckmann rearrangement might take place in more than one way. One process, the reaction series G, would involve the formation of an ammonium salt, its dehydration to yield a univalent nitrogen salt, and then rearrangement of the

positive ion of this salt. Another process would be the direct interchange of groups as suggested by Beckmann.

The univalent nitrogen mechanism as advanced originally by Stieglitz found many adherents, notable among them Schroeter, who offered a considerable amount of experimental work to verify this mechanism (91). Despite the stereochemical criticism of Montagne, the theory was reaffirmed by Schroeter (92) and re-advanced in essentially its original form by Houben (93) in 1921. Stieglitz' theory does offer the advantage of coördinating by a single hypothesis several different classes of carbon-nitrogen re-arrangements. It is, however, a debatable point whether this unified view is not arrived at by emphasizing formal similarities and neglecting essential differences. Certainly this feature of the theory in the hands of others than Stieglitz has led to some em-barrassing difficulties. For in order to emphasize the similarities between the various types of carbon-nitrogen rearrangements, several chemists have adopted the questionable expedient of referring to them all as Beckmann rearrangements. They have as a result found themselves in the awkward predicament of writ-ing about four types of Beckmann rearrangements, advancing a single theory (univalent nitrogen) to explain these four types of rearrangements, and then being forced to admit that the general explanation of the Beckmann rearrangement (in the wider sense) did not apply to the Beckmann rearrangement itself.

In concluding this discussion of the univalent nitrogen mecha-nism it should be pointed out that this mechanism offers no explana-tion for the *trans* shift. Furthermore, it is only fair to note that the difficulties to which we have called attention in the applica-tion of this mechanism to the rearrangement of ketoximes are not encountered when the mechanism is applied to other types of carbon-nitrogen rearrangements. The merits of the univalent nitrogen mechanism when dealing with the Hofmann, Curtius, and Lossen rearrangements should be considered quite apart from its merits when dealing with the Beckmann rearrangement.

At this place it will be advisable to depart from such chronolog-ical sequence as we have followed, in order to consider the work of Lachmann, who emphasized the view that salt formation is an

essential step in the Beckmann rearrangement (8). Lachmann, like Henrich (94) and Lehmann (7), showed that oxime salts rearranged. He then called attention to the equilibria existing in acid solutions of oximes, from which he concluded that even in an aqueous solution of an oxime it should be possible to bring about rearrangement if the hydrogen-ion concentration is sufficient to ensure the presence of the oxime as a salt.

$$\begin{array}{c}R \\ \diagdown \\ \diagup \\ R\end{array}CO + NH_2OH \rightleftharpoons \begin{array}{c}R \\ \diagdown \\ \diagup \\ R\end{array}C{=}NOH + H_2O$$

$$\begin{array}{c}R \\ \diagdown \\ \diagup \\ R\end{array}C{=}NOH + HCl \qquad \left[\begin{array}{c}R \\ \diagdown \\ \diagup \\ R\end{array}C{=}N\begin{array}{c}\diagup OH \\ \diagdown H\end{array}\right]^{+} Cl'$$
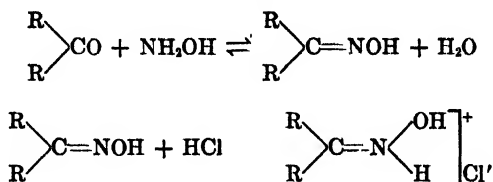
In conformity with this view Lachmann was able to effect the rearrangement of benzophenone oxime in aqueous solution (95). This fact led him to adopt essentially Beckmann's view of the rearrangement as a direct interchange of groups—this interchange, however, occurring according to Lachmann in the positive ion of the oxime salt rather than in the oxime itself, and no dehydration of the oxime salt being necessary to bring about rearrangement. No explanation was advanced to account for the fact that the interchange involves groups spatially distant from one another.

Review of the work of Kuhara

It is our next task to undertake a review of the work of Kuhara. This work, carried on during the fourteen years between 1906 and 1920, we shall consider in considerable detail both on account of its interest and because of its comparative inaccessibility (96). Kuhara's thesis, to state it at the outset in its simplest form, is that the acyl derivatives of oximes undergo rearrangement and that this rearrangement involves a direct interchange of spatially adjacent groups. This is, it will be noted, essentially Beckmann's idea of the direct interchange of groups with the reagent acting as a catalyst. However, according to Kuhara, the acyl derivatives of the oximes and not the oximes themselves rearrange, while the reagent which in one stage of the rearrangement functions as a

true catalyst actually takes part in a subsequent stage of the process. For example, Kuhara formulated the rearrangement of benzophenone oxime on treatment with acetyl chloride in the following fashion (97).

$$\begin{array}{ccc} C_6H_5CC_6H_5 & & C_6H_5CC_6H_5 \\ \| & + CH_3COCl \rightarrow & \| & + HCl \\ NOH & & NOCOCH_3 \end{array} \qquad (H)$$

$$\begin{array}{ccc} C_6H_5CC_6H_5 & & C_6H_5COCOCH_3 \\ \| & \xrightarrow{\ HCl\ } & \| \\ NOCOCH_3 & & NC_6H_5 \end{array} \qquad (J)$$

XIV

$$\begin{array}{ccc} C_6H_5COCOCH_3 & & C_6H_5CO \\ \| & + HCl \rightarrow & | & + CH_3COCl \\ NC_6H_5 & & NHC_6H_5 \end{array} \qquad (K)$$
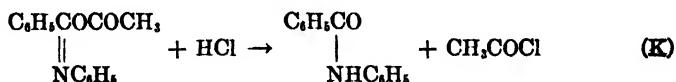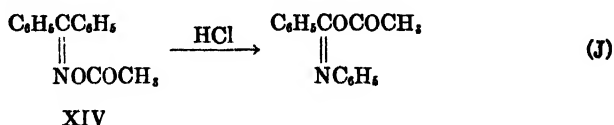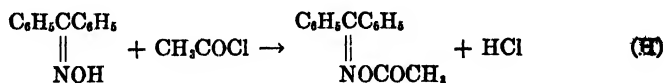
According to this view an oxime acetate (XIV) should rearrange if hydrogen chloride is present (reaction J), but since the hydrogen chloride takes part in and is used up by the subsequent reaction (K), it follows that a given quantity of hydrogen chloride should be capable of rearranging only an equivalent amount of an oxime acetate. In other words, considering the reaction in its entirety, the effect of the hydrogen chloride is not catalytic in the usual sense of the term. This, by experiment, was found to be the case. Using the acetate (XIV), the amount rearranged was found to be proportional to the amount of hydrogen chloride present.

By a continuation of his reasoning that the acyl derivatives of oximes rather than the oximes themselves rearranged, Kuhara came to the conclusion that the rates of rearrangement of a given oxime by a series of acid chlorides should be in the same order as the "negativity" of the acyl groups; in more precise terms, the rates of rearrangement of a given oxime by a series of acid chlorides should be in the same order as the strengths of the acids derived from these acid chlorides. This also was verified experimentally using benzophenone oxime (98) and acetophenone oxime (99) with acetyl chloride, chloroacetyl chloride, and benzenesulfonyl chloride. Some typical results obtained with benzophenone oxime are given in table 1.

Calculations made from data of the type presented in table 1 showed that the reaction being measured was of the first order.

TABLE 1

Rearrangement of benzophenone oxime by acid chlorides

TIME	BENZANILIDE FROM BENZOPHENONE OXIME		
	With CH_3COCl	With $ClCH_2COCl$	With $C_6H_5SO_2Cl$
minutes	*per cent*	*per cent*	*per cent*
10	0.0	61.0	93.2
60	26 9	70.7	—
120	43.9	76.9	—

Similar calculations from the rate of rearrangement of the acetate of benzophenone oxime by hydrogen chloride showed that here also the reaction measured was of the first order. At this point Kuhara revised slightly his method of formulating the rearrangement in favor of the following presentation.

$$
\begin{array}{c}
C_6H_5CC_6H_5 \\
\quad\quad\quad + CH_3COCl \xrightarrow{\text{rapid}} \left[\begin{array}{c} C_6H_5CC_6H_5 \\ \| \\ HNOCOCH_3 \end{array}\right]Cl \\
NOH
\end{array}
$$

$$
\left[\begin{array}{c} C_6H_5CC_6H_5 \\ \\ HNOCOCH_3 \end{array}\right]Cl \quad \xrightarrow{\text{slow}} \quad \left[\begin{array}{c} C_6H_5COCOCH_3 \\ \| \\ HNC_6H_5 \end{array}\right]C
$$

XV XVI

$$
\left[\begin{array}{c} C_6H_5COCOCH_3 \\ \| \\ HNC_6H_5 \end{array}\right]Cl \quad \xrightarrow{\text{rapid}} \quad \begin{array}{c} C_6H_5CO \\ \\ NHC_6H_5 \end{array} + CH_3COCl
$$
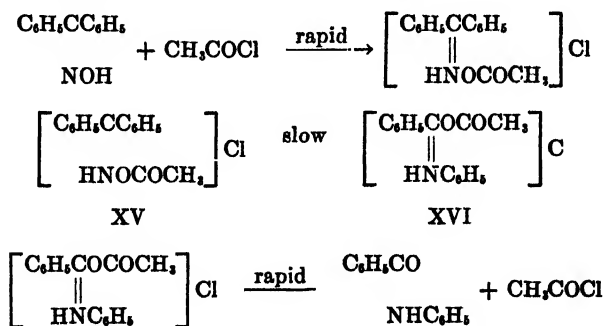
In his original publication Kuhara wrote the salts XV and XVI as XVII and XVIII, respectively.

$$
\begin{array}{cc}
C_6H_5CC_6H_5 & C_6H_5COCOCH_3 \\
\| & \| \\
HCl \cdot NOCOCH_3 & HCl \cdot NC_6H_5 \\
\text{XVII} & \text{XVIII}
\end{array}
$$
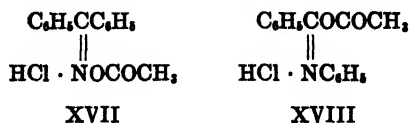
This method of formulating the rearrangement as involving an ammonium salt is not used consistently in Kuhara's articles and is not adhered to even in the discussion which accompanies its origi-

nal presentation (98), for in that discussion Kuhara states that
the rearrangement is essentially a shift of the following type.

$$\begin{array}{ccc} \text{RCR}' & & \text{RCOCOR}'' \\ \| \quad \uparrow\downarrow & \rightarrow & \| \\ \text{NOCOR}'' & & \text{NR}' \end{array}$$
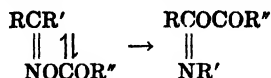
This change is accelerated by an increase in the temperature and
an increase in the hydrogen-ion concentration of the rearranging
medium. Further, the tendency of the acyl group to migrate is
conditioned by its "negativity," as measured by the dissociation
constant of the acid derived from the acyl group. This, according
to Kuhara, is shown by the fact that whereas the acetate of benzo-
phenone oxime (XIV) requires the presence of hydrogen chloride
to undergo rearrangement, the benzenesulfonate of benzophenone
oxime (XIX) rearranges even in alkaline solution—that is, rear-
rangement occurs on treatment of benzophenone oxime in sodium
hydroxide with benzenesulfonyl chloride. Apparently a fair
résumé of Kuhara's views at this time would be given by the state-
ment that the acyl derivatives of oximes rearrange as such if the
acyl group is sufficiently "negative," but if the acyl group does not
have sufficient "negativity" to bring about spontaneous rearrange-
ment, then salt formation is a necessary prerequisite to the proc-
ess. Kuhara would not, as we shall see later, admit that oxime
salts, as opposed to the salts of acyl derivatives of oximes,
rearranged.

In a very important paper Kuhara (100) investigated in detail
the action of benzenesulfonyl chloride on benzophenone oxime.
By operating carefully he was able to isolate the benzenesulfonate
(XIX) of that oxime and to establish its structure as such by
hydrolysis to the oxime and benzenesulfonic acid. The benzene-
sulfonate, a crystalline solid melting at 62°C., rearranged to yield
the ester (XX), instantaneously on melting, more slowly on
standing as a solid or by exposure, again as a solid, to ultra-violet
radiation. The ester, an oil, could be hydrolyzed by water to
furnish benzanilide and benzenesulfonic acid.

$$\begin{array}{ccc} \text{C}_6\text{H}_5\text{CC}_6\text{H}_5 & & \text{C}_6\text{H}_5\text{COSO}_2\text{C}_6\text{H}_5 \\ \| & & \| \\ \text{NOSO}_2\text{C}_6\text{H}_5 & & \text{NC}_6\text{H}_5 \\ & & \\ \text{XIX} & & \text{XX} \end{array}$$
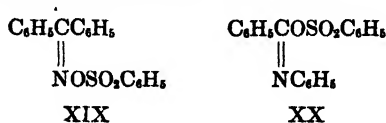
Kuhara also worked with oxime salts, the hydrochlorides of acetophenone oxime and of benzophenone oxime. These he found to undergo rearrangement on heating (12). In his attempt to interpret this behavior in the light of his view that rearrangement took place spontaneously when a sufficiently negative group was attached to the oximino nitrogen atom, Kuhara was forced to adopt Procrustean tactics in handling the facts. In his opinion the rearrangement of an oxime hydrochloride involved the following steps. (Kuhara, of course, wrote the hydrochloride in a fashion analogous to formula XVII.)

$$\begin{bmatrix} C_6H_5CC_6H_5 \\ \parallel \\ HNOH \end{bmatrix} Cl \rightarrow \begin{matrix} C_6H_5CC_6H_5 \\ \parallel \\ NCl \end{matrix} \rightarrow \begin{matrix} C_6H_5CCl \\ \parallel \\ NC_6H_5 \end{matrix} \rightarrow \begin{matrix} C_6H_5CO \\ | \\ NHC_6H_5 \end{matrix}$$

$$\qquad\qquad\qquad\quad XXI \qquad\qquad XXII$$
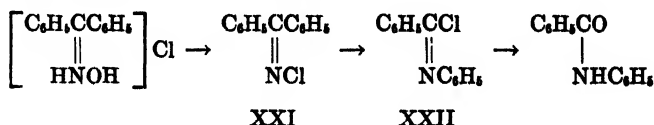
Kuhara was aware that Stieglitz and Peterson (82, 83) had already prepared the imino chlorides of ketones and had showed that they do not undergo a Beckmann rearrangement. To reconcile these facts with his theory, Kuhara was forced to make the experimentally unverifiable assumption that the intermediate (XXI) which he postulated contained a negative chlorine atom instead of the positive chlorine atom found in chloroimino ketones. A ketone chloroimide containing negative chlorine will, according to Kuhara, be incapable of isolation, since its one and immediate reaction will be rearrangement to furnish an imide chloride (XXII).

Mechanisms which account for a trans shift on rearrangement

Kuhara's mechanism, like all the other mechanisms which we have examined up to this time, makes no provision for the occurrence of a *trans* shift on rearrangement. There are a number of mechanisms, however, which either do attempt to take into account the *trans* shift or are capable of being extended so as to take it into account. These mechanisms have in common the feature of pictorializing the Beckmann rearrangement as a continuous process by the use of partial or residual valences. The earliest is that of Bucherer (47), who considered that in an oxime par-

tial valence forces are set up between the nitrogen atom and the hydrocarbon residue spatially distant from the oximino hydroxyl group.   As the strength of these partial valences increases so as to approximate an ordinary linkage the hydroxyl group shifts.

$$
\begin{array}{ccccccc}
\text{RCR}' & & \text{RCR}' & & \text{HOCR}' & & \text{OCR}' \\
\| & \rightarrow & \| & \rightarrow & \| & \rightarrow & | \\
\text{NOH} & & \text{NOH} & & \text{RN} & & \text{RNH}
\end{array}
$$
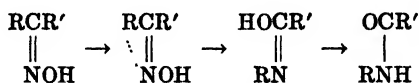
Similar views can be found in the papers of Biltz (101) dealing generally with the problem of organic rearrangements.   Meisenheimer (48), also, has suggested a pictorial view of the rearrangement in order to account for the *trans* shift.   In his view the attraction between the oximino hydroxyl group and the hydrocarbon residue spatially near it is sufficient to release partial valences on the nitrogen atom so that it eventually captures the hydrocarbon residue spatially distant from the hydroxyl group.   This leaves a gap molecule with free valences which then shifts to yield the final product.

$$
\begin{array}{ccccccccc}
\text{RCR}' & & \text{R-C-R}' & & \text{R-C-R}' & & \text{CR}' & & \text{HOCR}' \\
\| & \rightarrow & \| \quad \| & \rightarrow & \backslash\| \quad \| & \rightarrow & \| \quad \| & \rightarrow & \| \\
\text{NOH} & & \ldots\text{NOH} & & \text{NOH} & & \text{RNOH} & & \text{RN}
\end{array}
$$
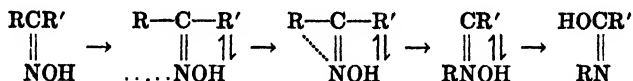
Perhaps the most definite of these pictorial mechanisms is that of Ramart-Lucas (102), who postulated the existence of single electron linkages or semi-valences.   Applied to the Beckmann rearrangement and in somewhat greater detail than is given in the original article we have:
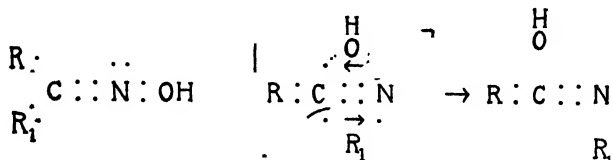
It is odd that at the time this view was put forward (1927) it was not presented as involving a *trans* shift for, superficially at least, as will be seen from the formulas to follow, it is far more easily represented in this fashion than in the way in which it was originally advanced.

$$
\begin{matrix} & H & \\ & O & \\ R\!:\!\!\!\cdot & \cdot\cdot & \\ & C::N: & \longrightarrow \\ R_1\!\!\cdot & & \end{matrix}
\left[\ R:C::N: \ \right]
\begin{matrix} & H & \\ & O & \\ & \cdot\cdot & \\ R:C::N: & \\ & R_1 & \end{matrix}
$$
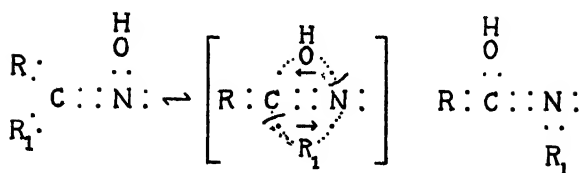
Classification of the mechanisms suggested for the Beckmann rearrangement

This concludes our survey of the mechanisms advanced for the Beckmann rearrangement. A summary of these mechanisms is now in order and for the purpose of this summary we shall divide the mechanisms into four general classes. This division into classes and the remarks to be made about the various classes will, it is believed, apply not only to the particular mechanisms which we are considering but also to a certain extent to the general problem of the mechanism of organic rearrangements. For in many, if not most, types of organic rearrangements the same four classes of mechanisms will be found to be advanced and, while in certain rearrangements one class of mechanism may be preferred, in general the merits and difficulties found in connection with the four classes as applied to the Beckmann rearrangement will also be found in connection with other rearrangements.

First to be considered is that type of mechanism, exemplified by Wallach's heterocyclic intermediate hypothesis, which seeks to avoid the necessity of admitting a direct interchange of groups or the direct migration of a single group. This end is to be accomplished by the use of intermediate compounds of such nature that the new linkage is established before the old linkage is destroyed. The intermediate compounds postulated by this theory employ only the normal valences of the atoms involved and are such as to be capable of isolation in appropriately chosen cases. We have seen that the one mechanism of this type advanced to account for the Beckmann rearrangement is experimentally untenable. After forty-five years of study of the Beckmann rearrangement with no success, it seems unlikely that this type of mechanism is capable of furnishing an adequate accounting for the processes involved in the rearrangement.

The second group of mechanisms to be considered is that group which attempts a formulation of the rearrangement on the basis of hypothetical intermediate compounds containing free valences —"Lückenmolekülen." The mechanisms of this group treat the rearrangement as a discontinuous process involving first the formation of a gap molecule and next the shift of one or more atoms or groups in that gap molecule to furnish the structural skeleton of the rearrangement product. The best example of this type of mechanism is furnished by the univalent nitrogen hypothesis of Stieglitz. This type of mechanism, in the opinion of the writer, offers little advantage. It is incapable of direct experimental test and it is so flexible that it is hardly possible to test the deductions which can be made from it. There is, it is true, a correspondence between theory and reality in that the correct end-products are predicted by the theory. Since, however, the prediction is made after the fact, it is of little significance. The advantage of this type of mechanism lies chiefly in providing a memory-aiding correlation of various types of rearrangements. It is an open question, however, whether this advantage is not too dearly purchased, for the gap molecule mechanism, by giving an apparent explanation of a set of phenomena, tends to discourage experimentation.[5]

The third group of mechanisms to be considered is exemplified by the views of Bucherer, Biltz, and Ramart-Lucas. (The mechanism advanced by Meisenheimer shares the characteristics of both the second and third groups.) The type of mechanism advanced by these chemists attempts, by the use of partial valences or single electron linkages, to represent the rearrangement as a continuous process. The comments made about the second group of mechanisms apply also to the present group, for the mechanisms of this latter group are also incapable of experimental verification and are of value chiefly as aids in visualizing rearrangements. One member of this group of mechanisms, that of Ramart-Lucas, offers a stimulating possibility. For, formulated in

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[5] As an example of the extent to which the idea of intermediates with free valences has been carried, attention may be called to a recent article by Schroeter (33). For a further general discussion of the usefulness of this type of mechanism see Hückel (103).

electronic terms instead of qualitatively by the use of partial valences, one may hope that it will become capable of experimental test with the increase in knowledge of atomic and molecular structure.

Finally there is the group of mechanisms, if mechanisms they may be called, which simply admit an interchange of groups and attempt to determine the point at which the interchange takes place. This was the original view of Beckmann, who held that the oximes themselves rearranged. It was also the view of Kuhara, who showed that the acyl derivatives of oximes rearranged, and the view of Lachmann who held that oxime salts rearranged. Common to all these is the admission of an interchange of groups with no statements about the way in which the interchange takes place. And in the present state of our knowledge of the Beckmann rearrangement we are justified only in such a restatement of the facts. We know that oxime salts rearrange. We know that the acyl derivatives of oximes rearrange. We know that the slowest reaction involved in the rearrangement is a reaction of the first order. And we know that rearrangement takes place between groups spatially distant in the oxime. Other than this we cannot speak with certainty about the Beckmann rearrangement.

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THE STEREOCHEMISTRY OF DIPHENYLS AND ANALOGOUS COMPOUNDS[1]

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CONTENTS

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[1] An attempt has been made in this communication to review all the important papers appearing in the field of the stereochemistry of diphenyl and related compounds, published prior to January 1, 1933 and the unpublished results of the senior author and his students.

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I. INTRODUCTION

Recent advances in stereochemistry have demonstrated the occurrence of numerous molecules not containing an asymmetric carbon atom but nevertheless resolvable into optically active antipodes. For example, compounds I (130), II (106), III (137), IV (126), and many other analogous ones have been resolved into their d and l forms. In these compounds, there is present no

I
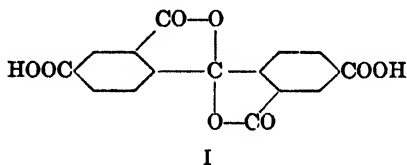
Ketodilactone of benzophenone-
2,4,2',4'-tetracarboxylic acid

III
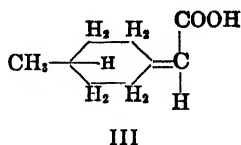
1-Methylcyclohexylidene-
4-acetic acid

II
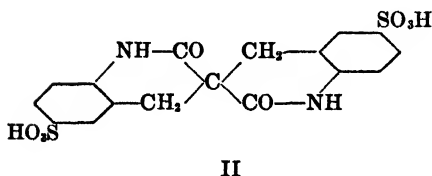
bis-Dihydrocarbostyril-3,3'-
spirane-6,6'-disulfonic acid

IV
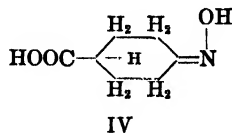
Oxime of cyclohexanone-
4-carboxylic acid

asymmetric carbon atom in the sense of the Le Bel-van't Hoff conception. However, an inspection of the space models of these molecules constructed with tetrahedral carbon atoms clearly indicates that such compounds do not possess either a center of symmetry, a plane of symmetry or an alternating axis of symmetry. Mirror images not superimposable upon the objects are, therefore, possible. Thus, in any consideration of the structural conditions necessary for the existence of optical isomers, it is the asymmetric character of the molecule as a whole

which is the determining factor. The broader aspect of the problem covers all cases of the optical isomerism of organic compounds and shows that the asymmetric carbon atom represents only a special case of asymmetry.[2]

Among all the known types of molecules not containing asymmetric carbon atoms which may exist in optically active forms, the one which has been most extensively investigated and from which fruitful and significant results have been obtained is that of certain diphenyl derivatives. The discovery and development of this field is curious and interesting and in the present résumé an attempt has been made to place the material in a logical order, with the historical development preserved as much as possible.

In this article the diphenyl derivatives, with the exception of those of benzidine and of diphenic acid, have been named as substitution products of diphenyl according to formula V.
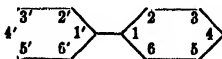
II. KAUFLER'S SPACE FORMULA

The relative position of the two benzene rings in diphenyl has been the subject of much speculative and experimental effort. Until 1907 it was usually considered that the two benzene rings in diphenyl and its derivatives were extended and coplanar. The early literature in organic chemistry contained the description of compounds derived from benzidine in which the two amino groups apparently acted similarly to those in o-phenylenediamine. It was possible, for example, to condense benzidine with anhydrous oxalic acid (22), with carbon disulfide (167), with phosgene (124), with phthalic anhydride (79), and N, N'-diethylbenzidine with phthalic anhydride (144), to give simple derivatives. To these compounds[3] the original discoverers assigned formulas VI,

[2] Conditions necessary for optical activity are clearly defined by Barker and Marsh (6a).

[3] There were other cyclic derivatives described in the literature such as thiocarbonyl and carbonyldianisidine (162), carbonyl-o-tolidine and oxalyl-o-tolidine (170), cycloformazyl methyl ketone (190), malonylbenzidine (140), and p-nitrobenzylidene benzidine (7).

VII, VIII, IX, and X. Another series of compounds obtained by Vaubel and Scheuer (183) were described as diazoimides with

$C_{12}H_{10}N_2C_2O_2$

VI

Oxalylbenzidine

VII
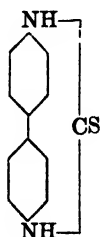
Thiocarbobenzidine
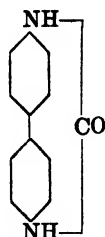
VIII

Carbonylbenzidine
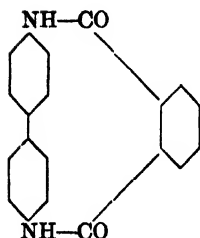
IX

Monophthalylbenzidine
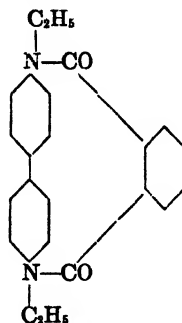
X

N,N'-diethylphthalylbenzidine

XI
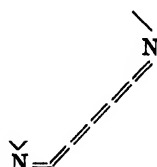
Diazoimidobenzidine

the general formula XI. Strakosch (167) recognized the possibility that thiocarbonylbenzidine might be a bimolecular compound, as shown in formula XII, but owing to the insolubility of this compound he was unable to determine its molecular weight.
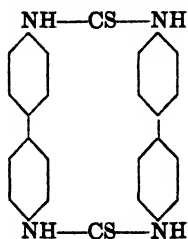
XII

In 1907 Kaufler (65) determined the molecular weight of the monophthalylbenzidine (IX) and found it to be unimolecular. He concluded that "for the other derivatives named, an analogous constitution was made very probable." As further evidence he prepared the products from phthalic anhydride and carbon disulfide with dianisidine, and he condensed p,p'-diaminodiphenylmethane and p,p'-diaminodiphenylethane with carbon disulfide. Several of these compounds were shown to be unimolecular (66, 67).

Since the two amino groups in benzidine or analogous diphenyls reacted so readily to form ring compounds similar to those formed with o-phenylenediamine, Kaufler (65) concluded that the two amino groups must be nearer together than was indicated by the ordinary formula (XIII), and proposed a more or less rigid folded space formula (XIV) for diphenyl.[4]   In this diagram (XIV) the

XIII   XIV
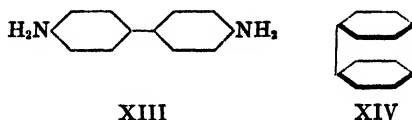
two rings are supposed to be lying in planes perpendicular to the plane of the paper, and the heavily printed lines indicate the sides of the hexagons which are nearer to the reader.

As further evidence for this conclusion Kaufler (65) pointed out that the diazotization of the second amino group of benzidine was more difficult than of the first amino group and also that after benzidine was tetrazotized, the second diazo group coupled with various dye intermediates with more difficulty than the first diazo group (147, 91).   One group produced a steric effect upon the other, such as might be expected if the substituents in benzidine and its tetrazonium salt were close together in space. Furthermore, Kaufler suggested that such a structure offered a simple explanation of the para coupling in the conversion of hydrazobenzene to benzidine.   Various investigators undertook further experimental tests of the Kaufler hypothesis.   These studies followed two lines: (1) further efforts to join the amino

[4] Kaufler's actual statement was that the two rings were "gegen einander geneigt." He also considered that naphthalene and other polynuclear molecules had a similar folded configuration.

groups of benzidine into a cyclic structure, and (2) the examination of the stereochemical implications of the folded structure.

(1) Many new derivatives of benzidine for which cyclic structures might be assumed, were prepared.   Unfortunately, in most cases no demonstration of the suggested structures was offered. The condensation products of benzidine with glyoxal, with benzil (32), with isophthalaldehyde, and with terephthalaldehyde (1) were assigned formulas XV, XVI, XVII, and XVIII. Both oxalic acid and phosgene reacted with 4,4'-diaminodiphenylmethane but yielded products (28) too insoluble to identify.
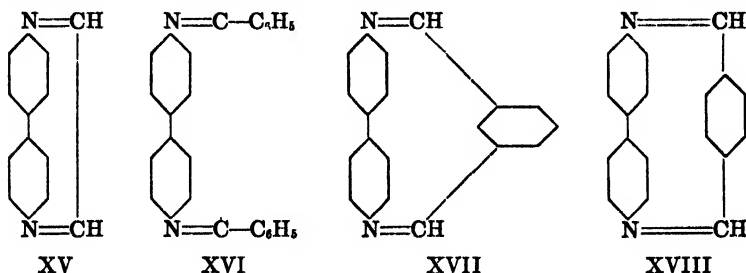
Morgan and his coworkers (131, 132) extended Vaubel and Scheuer's work on diazoimides (XII) by converting naphthalene-β-sulfonylbenzidine into a substance which was formulated as XIX.
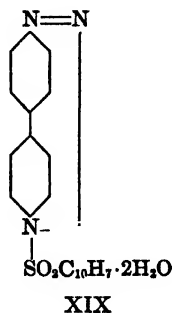
(2) From the stereochemical standpoint, the Kaufler formula made possible certain isomeric substituted diphenyls which otherwise would be non-existent.   There were two dinitrobenzidines described in the literature, one prepared by Strakosch (167) and

the other by Bandrowski (5). The former was shown definitely to be the 3,3'-dinitro derivative (XX) (26, 23), and the second apparently had the nitro groups in the same positions. In 1912, Cain and his coworkers (29, 30, 31) adopted the Kaufler structure to explain the existence of these conventionally inexplicable isomers; he called the one a 3,3'-dinitro derivative (XXI), and the other a 3,5'-dinitro derivative (XXII); further support of such a viewpoint resulted from the experiments of Brady and McHugh (23). Later, Cain reported the preparation of two pairs
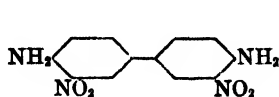
XX
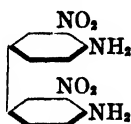
XXI

Bandrowski's
m.p. 233°

XXII

Strakosch's
m.p. 275°

3,3'-Dinitro-4,4'-
diaminodiphenyl
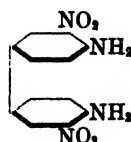
3,3'-Dinitro-4,4'-
diaminodiphenyl

3,5'-Dinitro-4,4'-
diaminodiphenyl

of geometric isomers of the *m*-dinitro-*o*-tolidines (169, 33)—
XXIII, XXIV, XXV, and XXVI. The results of these investigations conformed so perfectly to the theory that they greatly strengthened the Kaufler hypothesis.
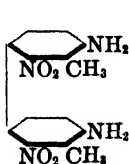
XXIII
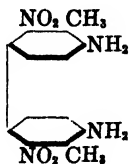
XXIV
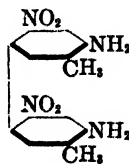
XXV
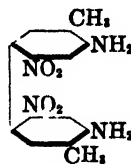
XXVI

Still another pair of stereoisomers was discovered. By oxidation of the nitration products of phenanthraquinone and also by direct nitration of diphenic acid, Schultz (146) obtained a dinitrodiphenic acid, which was later (145) demonstrated to be 2,2'-dinitro-6,6'-dicarboxydiphenyl (XXVII). When Kenner and Stubbings (71) attempted to prepare this acid by coupling the ester of 2-iodo-3-nitrobenzoic acid in the presence of copper

powder and saponification, they obtained a different acid. On reduction, Schultz's acid yielded the corresponding diamino acid, whereas Kenner's acid produced an internal dilactam with extraordinary readiness. Kenner and Stubbings concluded that these acids constituted a pair of geometric isomers and assumed that Schultz's acid was the *cis* form (XXVII) and their own compound was the *trans* form (XXVIII).

COOH COOH   COOH COOH   NO₂   COOH   CO—NH

NO₂   NO₂   NH₂   NH₂   COOH NO₂   NH—CO

XXVII   XXVIII

Schultz's acid   Kenner's acid
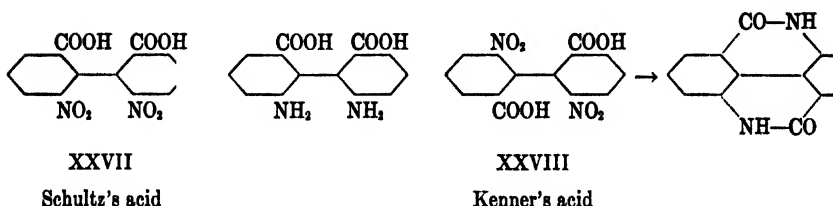
After the description of Cain's two dinitrobenzidines had been published, King (74) in an article entitled "The Possibility of a New Instance of Optical Activity without an Asymmetric Carbon Atom," pointed out that if Kaufler's formula were correct, one of Cain's dinitrobenzidines, the 3,5' derivative (XXII), but not the 3,3' (XXI) should be resolvable. Thorpe (171) also mentioned a similar possibility in one of the dinitrodiphenic acids prepared by Schultz and by Kenner and Stubbings. Kamm (63) attempted the resolution of diphenic acid, but without success.

Christie and Kenner (41) discussed further in some detail the stereochemistry of the three possible space formulas of the two dinitrodiphenic acids. On the basis of the coplanar formula for diphenyl, the *cis* form (XXVII) possessed a plane of symmetry and the *trans* form (XXVIII) had a center of symmetry, so that neither form should be resolvable into optical isomers. On the basis of the Kaufler formula, however, the *cis* form (XXIX) possessed a plane of symmetry but the *trans* form (XXX) did not, and a pair of mirror images should exist for this latter form. On the basis of formulas with a common axis for the two benzene rings but with the rings noncoplanar, both forms should be resolvable. The limiting case (XXXI) of this kind in which the planes of the two rings were at right angles was excluded, since it did not allow the existence of geometric isomers.

NO₂   NO₂

NO₂   COOH

COOH   NO₂

XXIX   XXX   XXXI
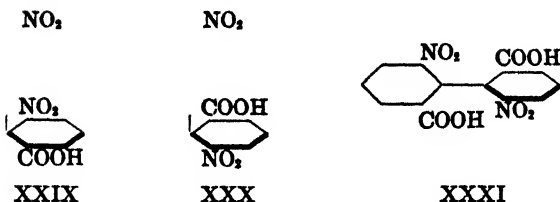
The climax of these stereochemical considerations was reached when Christie and Kenner (41) successfully resolved their dinitrophenic acid, the supposed *trans* form (XXX), into antipodal forms.[5] Very convincing support was thus given to Kaufler's formula for the diphenyl system.

In addition to all the chemical evidence in favor of Kaufler's hypothesis, an attempt was made to attack this problem by a physical method. Mack (111) calculated the average cross-sectional area of the diphenyl molecule from the diffusion coefficient and the result was in better agreement with the folded structure than with the extended formula.

In summary: There are six types of observations which were considered to receive explanation by means of Kaufler's formula, namely:—

1. The formation of cyclic derivatives of benzidine.

2. The existence of geometrical isomers of substituted diphenyls.

3. The optical resolution of substituted diphenic acids.

4. The inactivity of the second amino group in benzidine or of the second diazo group in tetrazotized benzidine.

5. The para conversion of hydrazobenzene to benzidine.

6. Physical data.

III. THE COLLAPSE OF THE EVIDENCE FOR THE KAUFLER FORMULA

In spite of the numerous experimental facts which supported Kaufler's view, other experiments which were intended to verify the folded formula but failed to do so, could not be overlooked.

[5] Soon after Christie and Kenner's discovery, five more diphenic acids of the same type were resolved and the phenomenon was regarded as supporting Kaufler's formula before the latter was abandoned. The resolution of these acids will be fully considered in a later part of this review.

Obviously, on the Kaufler hypothesis, the 4,4' and 3,3' positions must be almost as near together in space as the 2,2' positions. But in most cases reactions take place at the 2,2', positions only. It was shown that neither 3,3'-dicarboxydiphenyl (181) nor 3,3',- 5,5'-tetracarboxydiphenyl (27) formed an anhydride, that 4,4'-dibromodiphenyl did not condense with sodium (172), that 4,4'-diiododiphenyl did not form p,p'-diphenylene with copper (152),[6] and that 4,4'-dinitrodiphenyl did not give intramolecular azo or azoxy compounds (172). Benzidine did not condense with phenanthraquinone (32). When it reacted with acetylacetone or benzoylacetone (173), or anhydrides of naphthalic, camphoric, or quinolinic acid (155), two molecules of ketone or anhydride condensed with one molecule of the base or only one amino group was attacked, but no cyclic compound could be obtained. Again, if the 4,4' positions are close together, there is a reasonable probability that those types of reactions which involve the para migration of certain groups in simple benzene compounds, might also be exhibited by certain derivatives of diphenyl, the migrating group passing from the 4 to the 4' position. All attempts (139, 13, 14) along this line resulted in failure.

Bell and Kenyon (10a) have pointed out that the Kaufler formula involves some very awkward changes in configuration. For example, the following series of reactions would indicate the formation of a meso tetranitrodiphenic acid from dinitrophenanthraquinone, whereas actually a racemic, resolvable modification was obtained.
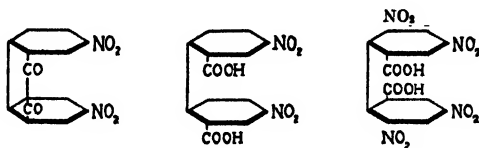
In considering these negative results, Adams (1) and also Adkins (2), as earlier investigators had intimated (69), pointed out that a fixed folded formula for all diphenyl derivatives was unten-

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[6] Sircar (153) described one of the products as tetraphenylene but this was proved by Kuhn (81) to be 4,4'-diphenyldiphenyl.

able, and that whether the rings were superimposed or extended possibly depended on the nature of the substituents.

Kenner and Mathews (69) and Morgan and Mickelthwait (132) questioned the structure of the condensation products of benzidine and α-diketones (XV, XVl) reported by Cain. The products differed in properties from the similar condensations of 2,2'-diaminodiphenyl with benzil. Upon reinvestigation of the benzidine derivatives, Ferriss and Turner (52) found them to be so complicated in character that no definite conclusions about structure could be drawn.

It was shown almost simultaneously by Turner (97, 98), Kuhn (89), and Sircar (154) and their collaborators that monophthalylbenzidine (IX), the most fully investigated Kaufler compound, had the constitution (XXXII)[7] rather than that (IX) hitherto
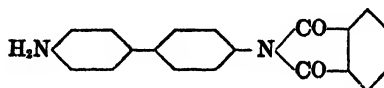
XXXII

assigned to it since it contained a free amino group, the presence of which was demonstrated by (1) condensation with various aldehydes, (2) condensation with another molecule of phthalic anhydride,[8] and (3) diazotization of the amino group and coupling with β-naphthol. Then Le Fèvre and Turner examined a number of other supposed ring compounds and found that oxalylbenzidine (VI) contained a free amino group; that the thiocarbonyl derivative (VII) was certainly XXXIII; that the carbonylbenzidine (VIII) was XXXIV (98, 99); that the N,N'-diethylphthalyl-

[7] Recently (55, 56) other structures were proposed for the monophthalylbenzidine, but they were proved by Turner (176) to be erroneous.

[8] Shimomura (151) formulated the change as being the conversion into structure
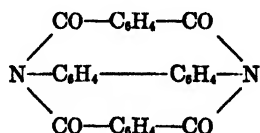
Formula XXXII explains this conversion in a normal manner.

benzidine (X) was not a chemical individual. Moreover, Cain's condensation product from benzidine and benzil was shown actually to be compound XXXV (98). A reëxamination of the compound to which Morgan assigned the formula XIX indicated that its properties were accounted for more adequately by formula XXXVI (98).

$$H_2N\langle\ \rangle-\langle\ \rangle N{=}C{=}S \qquad \left[H_2N\langle\ \rangle-\langle\ \rangle NH\right]_2 CO$$

<div align="center">XXXIII   XXXIV</div>

$$\begin{array}{c} C_6H_5{-}CO \\ | \\ C_6H_5{-}C{=}N\langle\ \rangle-\langle\ \rangle N{=}C{-}C_6H_5 \end{array} \qquad \begin{array}{c} COC_6H_5 \\ | \\ \end{array}$$

$$N{\equiv}N\langle\ \rangle{=}\langle\ \rangle{=}N{-}SO_2C_{10}H$$
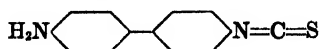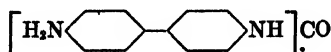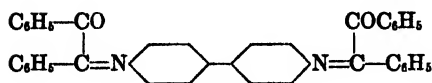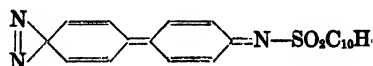
<div align="center">XXXV   XXXVI</div>

As for other products of a supposedly similar structure, they were either ill-defined compounds of unknown molecular structure or contained one free amino group (154, 50, 94). In none of these cases, as can be seen, were the two amino groups of the benzidine molecule combined in a ring, and thus the first set of phenomena which the Kaufler formula was intended to explain did not exist.

The question regarding the geometrical isomers next received attention. Le Fèvre and Turner (96, 95) proved that the most fully investigated of Cain's pairs of isomers, namely, the two dinitrobenzidines (XXI and XXII), were not stereoisomers but position isomers. Bandrowski's diamino compound was not the 3,3'-dinitro derivative but was impure 2,2'-dinitro-4,4'-diaminodiphenyl. And Cain's two pairs of isomers of dinitrotolidine were not XXIII, XXIV, XXV, and XXVI, but were the position isomers XXXVII, XXXVIII, XXXIX, and XL (100).

$$\begin{array}{c} CH_3 \qquad\quad CH_3 \\ H_2N\langle\ \rangle-\langle\ \rangle NH_2 \\ NO_2 \quad NO_2 \end{array} \qquad \begin{array}{c} CH_3\ NO_2 \quad NO_2\ CH_3 \\ H_2N\langle\ \rangle-\langle\ \rangle NH_2 \end{array}$$

<div align="center">XXXVII   XXXVIII</div>

$$\begin{array}{c} CH_3\ NO_2 \quad CH_3 \\ H_2N\langle\ \rangle-\langle\ \rangle NH_2 \\ NO_2 \end{array} \qquad \begin{array}{c} CH_3 \qquad\quad CH_3 \\ H_2N\langle\ \rangle-\langle\ \rangle NH_2 \\ NO_2 \quad NO_2 \end{array}$$
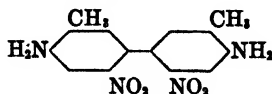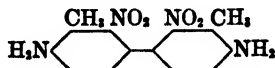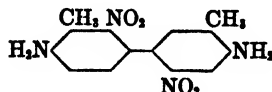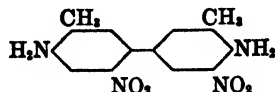
<div align="center">XXXIX   XL</div>

The reinvestigation (43, 39) of Schultz's acid (XXVII) led to the conclusion that it was not 2,2'-dinitro-6,6'-dicarboxydiphenyl but was its position isomer, 2,4'-dinitro-6,6'-dicarboxydiphenyl. Thus Schultz's acid and Kenner's acid were not stereoisomers, and Schultz's acid, previously regarded as probably belonging to the *cis* form, nonresolvable class, should be resolvable, and, in fact, was later resolved.   Therefore, the second important line of evidence, the existence of geometrical isomers, which was regarded as supporting the Kaufler formula, proved to be misleading on account of erroneous experimental results.

As mentioned previously, Kaufler considered that his formula, because of the steric hindrance effect of 4,4' groups upon each other, explained (1) the difficulty of diazotizing the second amino group in benzidine, (2) the slowness of coupling of the second diazo group in benzidinetetrazonium chloride, and (3) the para-hydrazobenzene–benzidine rearrangement.   There is considerable question whether the first difficulty exists (187).   Le Fèvre and Turner have assumed that the second is sufficiently explained by the insolubility of the intermediate monocoupled product[9] formed as the first step in the coupling of benzidinetetrazonium chloride (98).   In regard to the benzidine change there is little advantage in Kaufler's formulation, since the closeness of positions has no correlation with intramolecular rearrangement and certainly does not explain the semidine rearrangement which frequently takes place simultaneously with the benzidine rearrangement.

Mack's (112) conclusions from diffusion coefficients and collision area that diphenyl had the Kaufler formula, were based on certain assumptions which later proved to be erroneous.   More recent studies of this same investigator, with improved technique, have led him, on the basis of gas kinetic evidence, to favor the extended coplanar formula.

It has been pointed out by Carothers (34) and by Mascarelli (117) that an objection to the Kaufler formula which has never

[9] Information from an expert in benzidine dyes is that benzidinetetrazonium salts give in some instances soluble monocoupled products.   As a consequence the question as to this characteristic of benzidinetetrazonium salts may be considered as still lacking satisfactory explanation.

been emphasized is the necessity of bending a bond to an angle of 90°. With a Kekulé nucleus such a formula cannot be constructed, and each time that chemists adopt assumptions that cannot be reconciled with the Kekulé nucleus they encounter difficulties.

In the meantime several investigations were published, the results of which brought forward fresh valuable evidence opposed to Kaufler's view. Barber and Smiles (6) observed that the diphenylene disulfide (XLI) was obtained by oxidizing 2,2'-dithioldiphenyl (XLII). If Kaufler's view is accurate, 4,4'-dithioldiphenyl should also give a disulfide on oxidation. In fact, however, neither the 4,4'-dithiol- nor the 3,3'-dithiol-diphenyl yielded any such result.
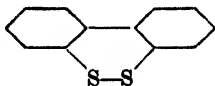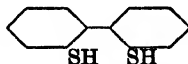
XLI   XLII

Kuhn and Zumstein (90) determined the dissociation constant of benzidine and compared it with the corresponding values for the three phenylenediamines. Their data indicated that the amino groups in benzidine were farther apart than Kaufler's formula suggested.

Williams and Weissberger (192) measured the dipole moments of several diphenyls. For a 4,4' symmetrically substituted diphenyl, any angle other than 180° between the axes of the rings should correspond to a definite dipole moment. They discovered, however, that in 4,4'-dichlorodiphenyl and 4,4'-dinitrodiphenyl, the moment was zero. Therefore, the rings were coaxial and could not be inclined toward each other.

The resolution of Kenner's dinitrodiphenic acid was followed by the resolution of several other diphenyls, but at the same time an even larger number of molecules which, according to the Kaufler formula should exist in enantiomorphic forms, resisted resolution.

A summary of this phase of the diphenyl problem shows that four of the six lines of evidence which supported the Kaufler

folded structure have been discredited and doubt has been thrown upon a fifth. Additional experimental data which are in better agreement with an extended formula have been obtained. The sole important remaining piece of evidence which is still experimentally sound, is the fact that several substituted diphenic acids do exist in optically active isomeric forms. It is, therefore, now possible to consider this phenomenon independently and seek a logical and correct explanation for it.

IV. OPTICAL ACTIVITY OF DIPHENYLS

Resolvable and nonresolvable diphenyls

The collapse of the evidence for the Kaufler formula left unchallenged Christie and Kenner's resolution of 2,2'-dinitro-6,6'-dicarboxydiphenyl into optically active forms. This opened an entirely new field of stereochemistry and experimental confirmation that certain other diphenyl derivatives could be resolved was speedily forthcoming. The optical antipodes of the following—XLIII, XLIV, Schultz's acid, and XLV—were among the first to be isolated:

O₂N<   NO₂ NO₂   >NO₂   O₂N<   NO₂   >NO₂
           COOH COOH   COOH COOH
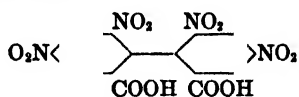
XLIII(41)   XLIV(42)

2,2',4,4'-Tetranitro-6,6'-   2,4,4'-Trinitro-6,6'-
dicarboxydiphenyl   dicarboxydiphenyl

NO₂   NO₂
        >NO₂
COOH COOH   COOH COOH

Schultz's acid(39)   XLV(14)

2,4'-Dinitro-6,6'-   2-Nitro-6,6'-dicarboxy-
dicarboxydiphenyl   diphenyl

At the same time, however, many compounds chemically and structurally closely related to the above diphenyls were found to be nonresolvable. Kamm (63) was unable to resolve diphenic acid (XLVI).

Bell and Kenyon (11) studied 2-carboxydiphenyl (XLVII), which formed well-defined brucine and morphine salts, without

any indication of resolution being obtained.   These authors (12) again attempted the resolution of diphenic acid, but unsuccessfully.   The dimenthyl diphenate and the d-β-octyl hydrogen diphenate (14) were nonresolvable.

2,2'-Dinitro-4,4'-dicarboxydiphenyl (XLVIII) was prepared by Bell and Robinson (15).   Its excessive insolubility militated against the production of uniform normal alkaloidal salts.   The acid liberated from the brucine salt was found inactive.   4-Nitro-2,2'-dicarboxydiphenyl (XLIX) (15) and 2-carboxy-2'-carbomethoxydiphenyl (L) were also found to be nonresolvable.

No active forms of 4,4'-dinitro-2,2'-dicarboxydiphenyl (LI) could be obtained, although its quinine salt had abnormal positive rotation which was considered by some chemists as evidence of the existence of the labile d form (83).

XLVI   XLVII   XLVIII   XLIX   L   LI
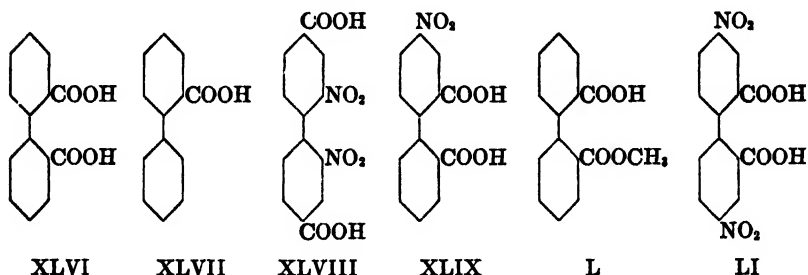
The compounds previously resolved were limited to those containing nitro and carboxyl groups.   Christie, James, and Kenner (40), by resolving 2,2'-dichloro-6,6'-dicarboxydiphenyl (LII), showed that no specific effect of the nitro group was involved and somewhat later Kenner and H. A. Turner (72) obtained active forms of 2,2'-dimethoxy-6,6'-dicarboxydiphenyl (LIII).

Cl   COOH   OCH₃ COOH   CH₃   NH₂

COOH Cl   COOH OCH₃   NH₂   CH₃
LII   LIII   LIV
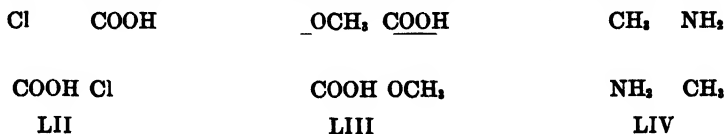
Possible sources of optical activity

At this stage of the development, several hypotheses concerning the cause of the peculiar optical isomerism were made possible.

Because all the resolvable compounds contained carboxyl groups, Phillips' views on active esters were considered. To account for the abnormal rotatory dispersion exhibited by some active esters, he (136a) postulated that the carbon atom in the carboxyl group might be an asymmetric center. For example, l-β-octylacetate could be written:

$$
\begin{array}{ccccc}
C_6H_{13}\ CH_3 & & C_6H_{13}\ CH_3 & & C_6H_{13}\ CH_3 \\
l\quad\diagdown\diagup & & \diagdown\diagup & & \diagdown\diagup\quad l \\
\overset{|}{CH} & & \overset{|}{CH} & & \overset{|}{CH} \\
\overset{|}{O} & \rightleftharpoons & \overset{|}{O} & \rightleftharpoons & \overset{|}{O} \\
l\quad \bar{O}-\overset{|}{C}^+ & & \overset{|}{C}{=}O & & {}^+\overset{|}{C}-O^- \quad d \\
\overset{|}{CH_3} & & \overset{|}{CH_3} & & \overset{|}{CH_3}
\end{array}
$$
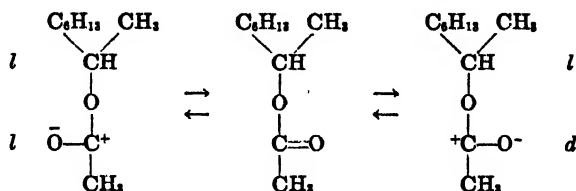
But the possibility of applying this theory to the stereoisomerism of diphenyls was entirely eliminated when Meisenheimer and Höring (121) were able to resolve 2,2'-dimethyl-6,6'-diamino-diphenyl (LIV). This resolution was confirmed by Mascarelli (114). It became apparent, then, that the optical activity of diphenyls was not associated with the presence of the nitro or the carboxyl group and the isomerism was probably not due to the specific effect of any individual group in the ring.

The possibility that a substituted benzene molecule is not necessarily a plane arrangement, led to the hypothesis that the optical activity might have its origin in the asymmetry of a single benzene nucleus. This viewpoint can hardly be maintained in the face of the absolute failure of numerous attempts to resolve substituted benzenes into optically active components (107).

A third theory was proposed by Turner (174), who attributed the phenomenon to the existence of para bonds; thus a substituted diphenyl would have the following formula (LV).

$$
\begin{array}{ccc}
R & & R \\
\overset{|}{CH{=}C} & & \overset{|}{C}{=}CH \\
\diagup\quad\quad\quad & & \quad\quad\quad\diagdown \\
HC{\longrightarrow}\quad C{-}C \quad{\longrightarrow}CH \\
\diagdown\quad\quad\quad & & \quad\quad\quad\diagup \\
CH{=}CH & & CH{=}CH
\end{array}
$$

LV
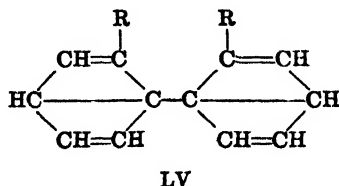
Turner pointed out that the molecule contained four asymmetric carbon atoms[10] and thus made optical isomerism possible. The formation of a tetraozonide of diphenyl was considered as a support of this hypothesis. According to this theory, however, more than one racemic form should exist and many of the nonresolvable compounds previously studied should be resolvable (110). This formula was criticized by Lowry (109a), and Turner later recognized this suggestion as untenable (179).

The coaxial-noncoplanar configuration

The fourth theory, that of coaxial but noncoplanar rings, was put forward by Christie and Kenner (41) and has now been generally accepted. It was assumed that the planes of the two benzene rings were at right angles to each other; under these conditions the following diagrams (LVI, LVII) represent the two active forms of a substituted diphenyl.
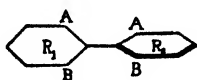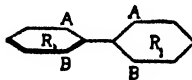
LVI   LVII

In each diagram, the R_1 ring is assumed to lie in the plane of the paper with the R_2 ring in a plane perpendicular to the paper. The two models are mirror images not superimposable. The case is comparable to that of allenic derivatives (LVIII and LIX) and to the spiranes. Thus, the optically active diphenyls represent one type of molecular asymmetry in which no asymmetric carbon atoms are present.
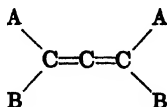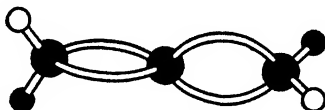
LVIII   LIX

---

[10] If the normal assumption is made that each of the two rings has its six carbon atoms in a plane, the para-bonded carbon atoms (so-called asymmetric by Turner) actually correspond to triple-bonded carbon atoms and no stereoisomerism in such molecules is structurally possible.—R. A.

But the coaxial-noncoplanar model alone is not sufficient, for if free rotation takes place about the bond joining the two nuclei, then the two rings could swing into a coplanar configuration and symmetry would be established and thus extinguish the optical activity of the compounds. To overcome this objection, one more postulate must be made, that of restricted rotation, a condition which was implied by Kenner.

V. THE THEORY OF RESTRICTED ROTATION

Fundamental assumptions

It is one of the fundamental assumptions in organic chemistry that two atoms joined by a single bond can have complete free rotation about the bond as an axis. Although Bischoff (18) suggested that complete rotation of carbon atoms could be hindered by substituents on them, no experimental evidence was offered for this view. But, without restricted rotation, Kenner's view of a coaxial-noncoplanar model for substituted diphenyls is impossible and, with restricted rotation, one of the commonly accepted principles of organic chemistry is violated.

Fortunately, the experimental material at this stage of the development is sufficient to give a clue to the essential feature of the problem. The formulas of several compounds, taken at random, are shown below. Those in the top line represent acids which have shown no capacity for resolution into enantiomorphs, while the formulas in the lower line represent compounds which have been obtained in optically active forms.

No resolution was attained with these acids.

(11)   (12)   (14)   (15)   (15)   (110)

NO₂   NO₂

O₂N   NO₂   Cl

COOH COOH COOH   COOH   COOH   COOH

COOH COOH   COOH   COOH

NO₂   Cl   COOH
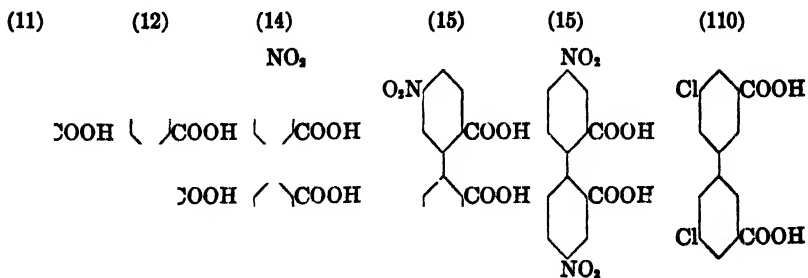
Compounds which were easily·resolvable:

(14)   (121)   (40)   (42)   (41)
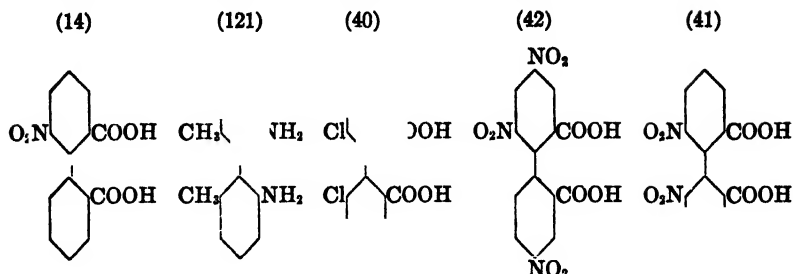
Inspection of these two sets of formulas reveals the difference between them.   Each of those which have been resolved into active forms has three[11] or four substituents in the 2,2′,6,6′ positions, while those not resolvable do not fulfil this condition.   It becomes evident that only properly substituted diphenyls can have coaxial-noncoplanar configurations.   In other words, the two rings in diphenyl rotate about the common axis and result in a coplanar structure unless there are proper substituents in the 2,2′,6,6′ positions.   This led to the theory of restricted rotation which was advanced almost simultaneously in slightly different forms by Turner and Le Fèvre (179), Bell and Kenyon (10), and Mills (125).

Essentially, the theory states that substituents in 2,2′,6,6′ positions in a diphenyl molecule can, by their interference, restrict the free rotation of the two nuclei around the common axis, thus preventing the rings from becoming coplanar and thereby producing in the molecule an asymmetric configuration.[12]

Various explanations

One immediately obvious merit of the theory is that it explains why all· the optically active diphenyls mentioned above possess at least three ortho substituents in the 2,2′,6,6′ positions; for only

[11] Now it is known that it is not the number but the size of ortho substituents which is of primary importance.   Recently several 2,2′ disubstituted diphenyls have been resolved.   This will be considered fully later.

[12] The model is by no means static, as pointed out by Mascarelli (115), since the semicircular oscillation of the two rings with respect to each other still may exist.

ortho substituents would be expected to be close enough to one another to give rise to the postulated restrictive influence. It is clear that two ortho substituents in one ring would hinder the ortho group or groups in the second ring from passing, and hence prevent the two rings from becoming coplanar. The ortho substituents, therefore, play an inhibiting rôle, just as two ortho substituents about a group in benzene exert "steric hindrance" effects in slowing down or stopping the normal reactions of that group (123).

With regard to the nature of the influence which inhibits free rotation of the two nuclei, opinions differed. Turner and Le Fèvre (179, 180) attributed the cause to the electrical nature of the substituted groups, the residual affinity on each ring, and the internuclear forces. According to their view, each carbon atom in the diphenyl molecule possessed a certain amount of free affinity. Carbon atoms $3,4,5$ and $3',4',5'$, and $6'$ would be mutually saturated in the Thiele sense, giving formula LX.

LX   LXI

LXII
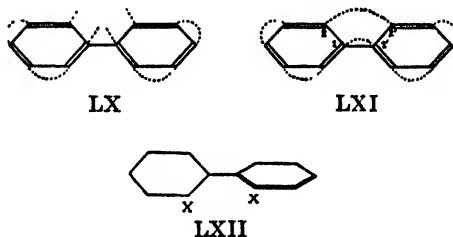
Since there was no reason to assume that the distance between carbon atoms 1 and 1' was greater than that between carbon atoms 1 and 2, some mutual saturation may occur between 1 and 1'. In this way the bond 1—1' became of the type existing in an ordinary benzene ring, and a tendency for rotation would appear to be to some extent diminished. Carbon atoms 2 and 2' would possess some free affinity, and this would tend as the major influence to stabilize the plane configuration as indicated in formula LXI. With a compound having two mutually repelling groups in positions 2 and 2', this mutual repulsion may be (1) equal to, (2) greater than, or (3) less than the original attractive

force between 2 and 2'.   In case 1 there would be a tendency for free rotation; in case 3 the effect would be as in diphenyl itself, though less marked.   In case 2, since there is now a repulsion and not an attraction between the 2 and 2' positions, distortion of the coplanar configuration may occur.   One benzene ring would rotate about the common axis through an angle, the magnitude of which would be a function of the repulsive force.   Thus results a coaxial-noncoplanar configuration (LXII).

Bell and Kenyon (10) suggested that, owing to their electrical characteristics or to their size, or to both, two ortho groups, A and B, acted as "obstacles" to the passage of an ortho group, C, on the other nucleus, thus preventing interconversion of the optical antipodes.
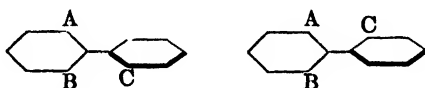
Mills (125), on the other hand, accepted the purely mechanical idea of steric hindrance and considered merely the bulk of the substituents.   A model built up from the usual tetrahedra and drawn to scale, indicated that two bulky ortho substituents in the one ring would interfere with the free rotation of the second ring, owing to collisions between them and the third ortho substituent. Thus, in 2-chloro-6,6'-dicarboxydiphenyl (figure 1) the carboxyl group attached to the lower nucleus could pass neither the chlorine atom (large shaded circle) nor the other carboxyl group, and hence was confined to a limited region in front of the plane of the upper ring.   On the other hand, if two of the groups were small, then free rotation was possible.   This complied with the facts in the case of the diphenic acids, for in these compounds the two ortho hydrogen atoms were not bulky enough to prevent the free rotation of the two rings about their common axis.

The obstacle or mechanical theory received support from Meisenheimer, Kuhn, Mascarelli, Adams, and others, and is now the more or less generally accepted viewpoint.   This theory has in recent years been put to rigid test, especially by Adams and his students, and an attempt has been made to put it on a semi-

quantitative basis from which predictions about resolvability, nonresolvability, and even optical stability of diphenyl derivatives might be made with a fair degree of accuracy.

Application of x-ray data

The application of values of atomic size obtained by physical measurements to the diphenyl problem was a natural development. Meisenheimer (121) first used atomic dimensions inferred from x-ray data to demonstrate the probability of collision between the amino and methyl groups in 2,2'-dimethyl-6,6'-diaminodiphenyl.
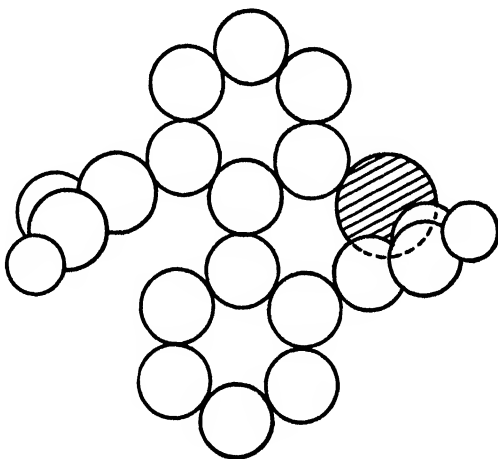
FIG. 1

Data intended to permit definite predictions concerning the resolvability of any given diphenyl were first presented by Stanley and Adams (158). On the obstacle theory the amount of interference will be determined by the size of the substituent atoms or groups. This magnitude, for the purposes in view, is not capable of being directly measured. It is possible, however, with the aid of certain assumptions to derive values which may reasonably be supposed to furnish a relative measure of the degree of interference. Distances between the centers of mutually combined atoms in the aliphatic series are known from x-ray data. These

values, slightly adjusted to bring them into line with aromatic compounds, are the "internuclear distances" for atoms shown in table 1. Similar "internuclear distances" for the groups CH_2, NO_2, etc., were obtained by adding to the value for the central

TABLE 1

Distance in Å. from the nucleus of the carbon atom of the benzene to center of group atom or

C—H	0.94	C—CH$_2$	1.73
C—F	1.39	C—Cl	1.89
C—OH	1.45	C—NO$_2$	1.92
C—COOH	1.56	C—Br	2.11
C—NH$_2$	1.56	C—I	2.20
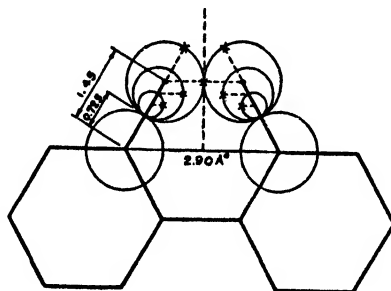
Fig. 2

TABLE 2

'Interference values" of certain pairs of atoms or groups

GROUPS AT 2,2' POSITION	INTERFERENCE OVER 2 90 Å.	GROUPS AT 2,2' POSITION	INTERFERENCE OVER 2 90 Å.
H, H	−1.02	F, NH$_2$	+0.05
COOH, H	−0.40	F, COOH	+0.05
Cl, H	−0.07	Cl, COOH	+0.55
NO$_2$, H	−0.04	NO$_2$, COOH	+0.58

atom an estimated quantity for the atoms attached to it. These values are used in the following manner. The vertical distance between the $2,2'$ ring carbon atoms when coplanar has been measured accurately and found to be 2.90Å. (51) (figure 2). The difference between this value and the sum of the "internuclear

distances" of the atoms or groups attached to the 2,2' carbon atoms was called the "interference value" and adopted as a measure of the relative degree of interference that might be expected.   Interference values for various atoms and groups are shown in table 2.   These values in table 2 indicate absence of interference in the first four pairs, slight interference in the next two pairs, and relatively large interference in the last two pairs. In other words, compounds containing the first four pairs should not be resolvable, those containing the next two pairs should be capable of resolution but easily racemized, and those containing the last two pairs should be easy to resolve and difficult to racemize.   Examples arc given below.

(nonresolvable)   (easily racemized)   (nonracemizable)
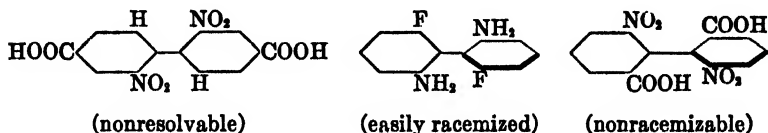
Naturally, interferences on each side of the diphenyl molecule are necessary to prevent rotation, and the above values indicate the expected interference only in molecules which are symmetrically substituted in the 2,2',6,6' positions.   In those cases where the calculated interferences are different on each side of the molecule (LXIII), the rate of racemization could be indicated in one of two ways—either by selecting the smallest of the values which show interference, or by selecting the average interference value of the two sides of the molecule.   By way of illustration, formulas LXIV and LXV may be compared.

LXIII   LXIV   LXV
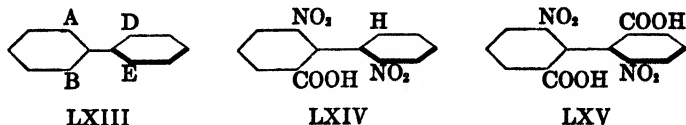
In LXIV the two interferences are NO_2—COOH, 0.58Å. (1.92Å. + 1.56Å. = 3.48Å. − 2.90Å. → +0.58Å.), or NO_2—NO_2, 0.84Å. (1.92Å. + 1.92Å. = 3.84Å. − 2.90Å. → +0.84Å.).   The relative interference value for this molecule by the first method would be +0.58Å.   Where the second procedure is followed,

interference in the molecule would be + 0.27Å., the average of
the interferences of NO_2—COOH and NO_2—H (on one side NO_2—
COOH, +0.58Å. and on the other NO_2—H, 1.92Å. + 0.94Å. =
2.86Å. − 2.90Å. → −0.04Å.).[13]   In the compound LXV either
method gives the same value, 0.58Å.   Experimentally LXV was
stable to racemization, whereas LXIV racemized in boiling
solution, thus indicating that the interference was not the same in
both molecules and that the average interference probably repre-
sented a more appropriate value.   A similar method of calcula-
tion would be equally suitable for 2,2′,6,6′-tetrasubstituted
compounds where the two sides of the molecule were not
symmetrical.

The estimated interferences paralleled, to a surprising degree, the
relative racemization rates as found experimentally and,therefore,
served admirably for the intended purpose.   Thus, when the
calculated interference was a minus quantity, in no instance was
it possible to resolve the molecule; when the value was slightly
above zero the compounds were resolvable but very readily
racemized, or in some instances merely mutarotating salts were
obtainable; when the value was considerably above zero, the
compounds were resolvable.   The rates of racemization of the
active isomers of this last type varied widely but paralleled the
relative interference value.

In the case of the tri- and di-substituted compounds, where one
or two hydrogens were present in the 2,2′,6,6′ positions, the rate
of racemization appeared to be greater than that expected from a
study of the tetrasubstituted compounds.   Greater mobility and
possibility for distortion of the molecule during oscillation so as
to let the groups slip by each other may be the explanation of this
discrepancy.

The arbitrary selection of the distance from the carbon atom
of the ring to the center of the atom or group attached, as an
expression of the relative interference effect of an atom or group,

---

[13] For estimating the average interference value in a compound like LXIV, it
is convenient merely to compare half the sum of the distances C—A, C—B, C—D,
C—E with 2.90.   If such a sum is larger than 2.90Å, the compound will, most
probably, be resolvable.

and a comparison of the sum of the values of the 2,2' groups with 2.90 to obtain interference values were made after a consideration of the geometry of a diphenyl molecule.

Figure 2 represents a diphenyl molecule with 2,2' substituents in which the dots indicate the centers of substituted atoms or groups. It is obvious that with atoms or groups the radii of which are 0.725Å., a collision might be expected. With atoms or groups of larger radii interference of varying degree should result. With atoms or groups of smaller radii no interference should occur. Since the sum of the internuclear distances of the 2,2' atoms or groups is equal to, is a little more than, or is a little less than 2.90, these differences were chosen as probably representing interference values which might approximate the actual interference of the substituents.

The method of calculating interference values described above involves assumptions to which theoretical objections can be raised. Various other methods of calculation might be used. Lesslie and Turner, for example, have recently presented for certain diphenyls models similar to those of Mills in which the atoms are drawn as spheres and to scale. Lesslie and Turner have criticized the method of calculation described above. Their method is, however, also open to criticism since it involves arbitrary assumptions as to the effective diameter of certain atoms (i.e., as to how close atoms can approach without interfering). The method of Stanley and Adams has the advantage of being simple to apply and, as has already been pointed out, of leading to conclusions in accordance with the observed facts.

VI. EXPERIMENTAL EVIDENCE FOR THE COAXIAL-NONCOPLANAR MODEL

The conception of the coaxial-noncoplanar configuration and the theory of restricted rotation are more or less inseparable. Actually the former is much more fundamental and the latter supplementary. Experiments which may verify the restricted rotation theory incidentally will prove the noncoplanar configuration. On the other hand, those investigations which offer merely additional evidence in favor of the noncoplanar model may

advantageously be considered separately for the clarity of presentation.

Resolution of compounds containing fused carbocyclic nuclei

The first extension of the stereoisomerism of diphenyl was into fused ring systems; if the coaxial-noncoplanar view be correct, properly substituted dinaphthyls, dianthranyls, and other molecules of a similar character should show optical isomerism. Kuhn and his students (85, 86, 87) resolved LXVI, LXVII, and LXVIII.
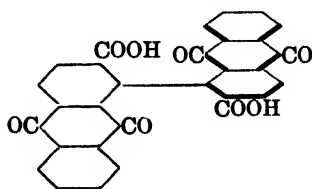
LXVI

2,2'-Dicarboxy-1,1'-
dianthraquinonyl
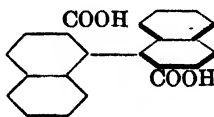
LXVII

2,2'-Dicarboxy-1,1'-
dinaphthyl
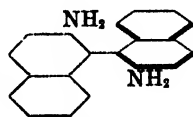
LXVIII

2,2'-Diamino-1,1'-
dinaphthyl

Mascarelli (115) discussed the theoretical possibilities among dinaphthyl and phenylnaphthyl derivatives.

Stanley and Adams (157) separated LXIX into optical antipodes.

Murahashi (134) obtained the active forms of LXX, and Lesslie and Turner (103) prepared and resolved a substituted phenyl-α-naphthyl (LXXI).
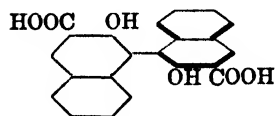
LXIX

2,2'-Dihydroxy-3,3'-dicar-
boxy-1,1'-dinaphthyl
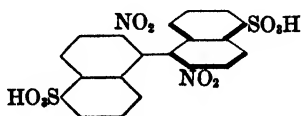
LXX

2,2'-Dinitro-1,1'-dinaph-
thyl-5,5'-disulfonic acid
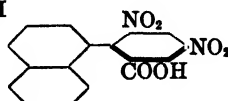
LXXI

3,5-Dinitro-6-naph-
thylbenzoic acid

All these results show that optical activity persists in properly substituted fused carbocyclic systems. The active forms of all of these compounds exhibited relatively high rotation and were stable to any ordinary methods of racemization.

Elimination of optical activity through 2,2' ring closure

One of the most interesting and convincing pieces of evidence demonstrating the noncoplanar structure for substituted diphenyls was accomplished through a study of certain 2,2',6,6'-substituted diphenyls which contained groupings capable of producing rings through the 2,2' positions. When 2,2'-dimethyl-6,6'-diaminodiphenyl (LIV) was acetylated, the introduction of acetyl groups did not effect any noticeable racemization. The diacetyl compound, in turn, was oxidized to the dicarboxylic acid which still possessed optical activity. But when the latter was hydrolyzed by cold acid, an inactive dilactam (LXXII) was obtained (121).

d   *d*   *d*

LIV
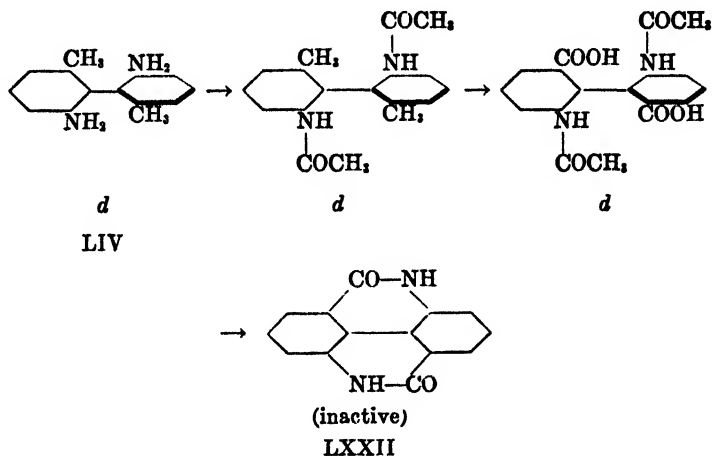
(inactive)

LXXII

The same phenomenon was noticed in 2-nitro-6,6'-dicarboxy-diphenyl, the *d* form of which produced the corresponding optically inactive fluorenone (LXXIII) when it was warmed with sulfuric acid. The fluorenone could not be resolved (15, 88, 182).

d   (inactive)

LXXIII

4-Carboxy-5-nitrofluorenone
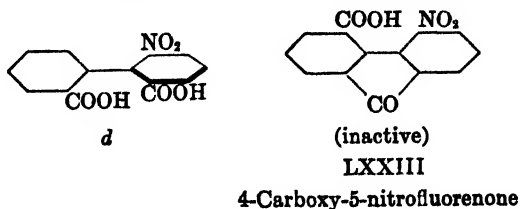
Kuhn and his students (86, 87) made a similar observation in the case of the dinaphthyl (LXXIV) which, upon heating with sulfuric acid, yielded inactive anthanthrone (LXXV). Inactive naphthocarbazol (LXXVI) resulted when either the *d* or *l* form of 2,2'-diamino-1,1'-dinaphthyl (LXVIII) was heated with hydrochloric acid.
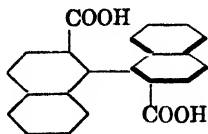
LXXIV
2,2'-Dicarboxy-1,1'
dinaphthy!
(active)
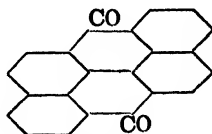
LXXV
(inactive)
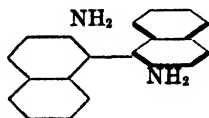
LXVIII
(active)
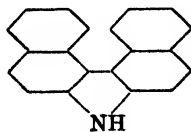
LXXVI
(inactive)

In all these cases five- or six-membered rings were formed linking the 2 and 2' positions. The disappearance of optical activity cannot be attributed to racemization, since most of these optical isomers are stable toward heat or toward many chemical reagents. It is due most probably to the change from a spatial arrangement to a coplanar structure. Before the 2 and 2' positions are linked in a ring the molecule has the coaxial-noncoplanar configuration. On the basis of the present knowledge of the stereochemistry of ring compounds, five- or six-membered rings[14] have the atoms in a single plane. As soon as the 2 and 2' carbons are linked by such a ring system, the two halves of the molecule are forced into a coplanar configuration. Thus a plane of symmetry is introduced into the molecule and optical activity disappears.

[14] This would, of course, not apply to saturated six-membered rings. All six-membered rings referred to in the diphenyls, however, would contain two C=C linkages, one from each of the benzene rings.

It is accepted that rings larger than six-membered are ordinarily strainless and the atoms do not lie in a single plane. If the 2 and 2′ positions in a resolvable diphenyl derivative are linked, therefore, in a strainless ring, the two nuclei of the molecule can still be noncoplanar and the potential optical activity can remain. This was demonstrated by the condensation of d-2,2′-diamino-1,1′-dinaphthyl with benzil with the formation of a highly active product (LXXVII) (87, 168). In this case the 2,2′ carbons are in an eight-membered ring.
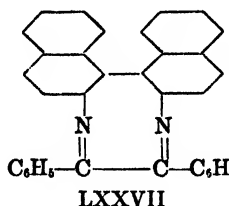
LXXVII

Sako (141a) has reported the preparation from active 2,2′-dimethyl-6,6′-diaminodiphenyl (LIV) of two derivatives (LXXVIIIa and LXXVIIIb) in which seven-membered rings are formed through the two amino groups. Both these compounds were optically active.

LXXVIIIa
7,8-Dimethyl-2-keto-2,3-dihydrodiphenylimidine
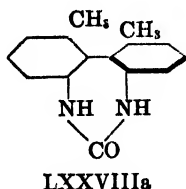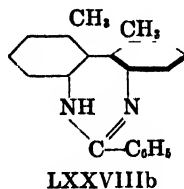
LXXVIIIb
7,8-Dimethyl-2-phenyldiphenylimidine

Unsymmetrical substitution in each ring

It is implied in the coaxial-noncoplanar model that each ring in a diphenyl must be unsymmetrically substituted in itself in order that the mirror images may not be superimposable and the compound may, therefore, be capable of resolution. When the coaxial-noncoplanar theory was first suggested, the active compounds known at that time, and even those prepared directly

afterward, contained different groups in the 2,2' or 6,6' positions and are represented by Series 1 of the general formulas listed below.

Series 1.
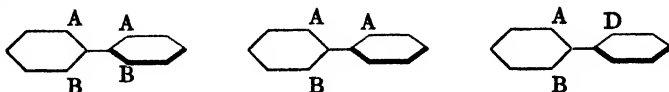
Series 2.
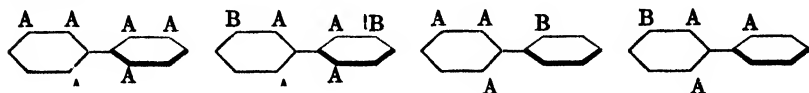
It was pointed out more specifically by Mascarelli (116) and by Hyde and Adams (62) that a benzene nucleus could be unsymmetrically substituted in several ways. All of the 2,2',6,6' positions could be occupied by identical atoms or groups, provided other substituents were present in the proper positions to render each ring unsymmetrically substituted. Formulas of Series 2 represent a few of the possibilities in molecules containing identical ortho substituents.

Adams and his students (133, 191, 19, 163) resolved a number of these—LXXVIII, LXXIX, LXXX, and LXXXI.
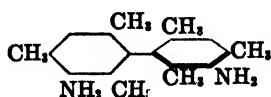
LXXVIII

3,3'-Diamino-2,4,6,2',4',6'-
hexamethyldiphenyl
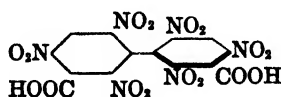
LXXIX

3,3'-Dicarboxy-2,4,6,2',4',6'-
hexanitrodiphenyl
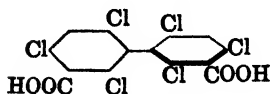
LXXX

3,3'-Dicarboxy-2,4,6,2',4',6'-
hexachlorodiphenyl
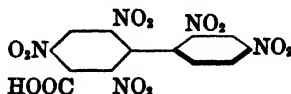
LXXXI

3-Carboxy-2,4,6,2',4'-
pentanitrodiphenyl

The active forms all proved to be exceedingly stable.

The general viewpoint of a coaxial-noncoplanar structure for these diphenyls, with the supplementary assumption of unsym-

metrical substitution in each ring, was so quickly and generally adopted that, until recently, no experiments had been performed to show that a properly but symmetrically substituted diphenyl would not be capable of resolution. The resolution of a diphenyl with symmetrical substitution would render the coaxial-non-coplanar theory impossible.

Experiments of Adams and his students in the course of their researches resulted in the preparation of several tri- and tetra-substituted compounds in which one ring was symmetrically substituted, and in no instance was resolution accomplished. Van Arendonk and Adams (185) were able to resolve LXXXII into active components but not LXXXIII, and additional examples are cited in the later sections on diphenylbenzenes and phenylpyrroles that symmetrical substitution in the rings destroys the optical isomerism.

NO_2 OCH_3 NO_2 NO_2 OCH_3

COOH OCH_3 COOH OCH_3

LXXXII   LXXXIII

2,3'-Dinitro-6-carboxy-2',6'-   2-Nitro-6-carboxy-2',6'-
dimethoxydiphenyl   dimethoxydiphenyl
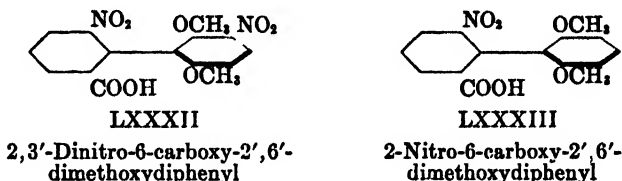
Physical data

Certain physical data have appeared which support the non-coplanar conception. From an x-ray study Clark and Pickett (46) drew the conclusion that in certain 2,2',6,6' derivatives of diphenyl, the two rings were in planes turned from each other at an angle not greater than 45°, while the rings in diphenyl itself were coplanar.[15]

Bergmann and Engel (17) made dipole measurements upon optically active 2,2'-diamino-6,6'-dimethyldiphenyl (LIV). Of the three possible formulas given below, LIVb, which is coplanar, should give no moment, while LIVc, also coplanar, gives a calcu-

---

[15] These data of Clark and Pickett have been criticized as insufficient to establish this particular truth, owing to the complexity of the organic molecules (45, 61), but just recently, after more experimental work in the laboratories of the Royal Institute in London, the conclusions of Clark and Pickett appear to be correct.

lated moment of 1.99×10^{18}. The value actually found was 1.66 $\times 10^{18}$ thus offering evidence for formula LIVa. These authors calculated from their measurements that the angle of the two planes in this molecule was 67°.
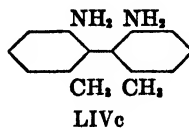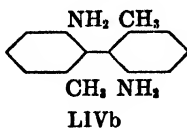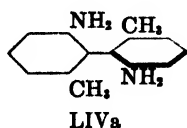
VII. EXPERIMENTAL EVIDENCE RELATIVE TO THE SIZE OF THE 2,2′,6,6′ GROUPS

The next important problem resolves itself into the determination of the mechanism by which various groups located in the 2,2′,6,6′ positions can prevent free rotation of the nuclei. The most obvious factors to be considered are (1) the size of the 2,2′,6,6′ groups, (2) the electrical nature of these groups, (3) the influence of atoms or groups not in the 2,2′,6,6′ positions. This section deals with the first two of these and the third is discussed in the following section.

On the basis of the obstacle theory, it should be possible merely by properly modifying the size of the 2,2′,6,6′ groups to prepare optically active diphenyls with widely varying degrees of stability to racemization. The racemization of active diphenyl derivatives or mutarotation of their salts may be explained on the basis of the theory of restricted rotation, in that thermal agitation causes the groups in the 2,2′,6,6′ positions to slip by each other and thus to result in complete rotations of the two nuclei.

The study of the comparative rates of racemization of different active diphenyls offers a semi-quantitative approach to the determination of the importance of the size of the groups in relation to the blocking effect. Up to 1930 all the known ortho-tetrasubstituted resolvable diphenyls were found to be highly antipodally stable, for instance, XXXI, LIV, LXIX, and LXXVII could not be racemized in boiling acid, alkaline or neutral solution. On the other hand XLIV, XLV, and Schultz's acid, the trisubstituted compounds, were found to racemize in boiling solutions.

The difference between these two sets of compounds is rather to be expected from the obstacle theory. The small volume of the hydrogen atom present in the trisubstituted diphenyls should lend much more chance for the nuclei to pass through the common plane and thus for one active form to change into the mirror image. Moreover, Stearns and Adams (163) pointed out the greater possibility in trisubstituted compounds of the rings bending toward each other when approaching the same plane so as to allow free rotation. This may be a factor in the gradual racemization of such compounds at higher temperatures.

Four pertinent and interesting phases of this problem have been studied experimentally. (A). It should be possible to prepare 2,2',6,6'-tetrasubstituted diphenyls which, unlike those at first studied, are nonresolvable or resolvable but easily racemized, provided the substituents are not sufficiently large or barely large enough to restrict the free rotation. On the other hand, a trisubstituted compound with large groups should be immune to racemization. (B). A comparison of the rates of racemization of a series of diphenyls in which two of three substituents or three of four substituents in the 2,2',6,6' positions remain constant and the third or fourth is varied, should furnish the method for a reasonably quantitative study. The rates of racemization should become greater as the sizes of the groups become smaller. (C). 2,2'-Disubstituted diphenyls or even 2-monosubstituted diphenyls should be capable of existing in optically active forms, provided the substituent or substituents are sufficiently large to collide with the hydrogen atoms, which appear to have a smaller size and blocking effect than any other atom or group. (D). In groups containing more than a single atom, the steric influence of that whole group should be affected to a greater or less extent by the size and character of those atoms or groups combined to the atom which is attached to the ring.

Each of these lines of attack will be discussed in order. From the practical standpoint the problem of studying the desired effects lies in the selection of the proper groups to substitute in the diphenyl and the preparation of such molecules. Evidence from many sources indicates the fluorine and hydroxyl or methoxyl

to be two of the smallest atoms or groups except hydrogen, with the amino and carboxyl groups not much larger.

Nonresolvable 2,2',6,6'-tetrasubstituted compounds

(A). The following representatives of Type A (LXXXIV, LXXXV, LXXXVI, LXXXVII), have been prepared by Adams and his students (77, 49, 9), and their resolution has been attempted by means of various alkaloid salts—brucine, strychnine, morphine, cinchonine, and quinine.

Cl   F   F   COOH

HOOC   F   F   Cl
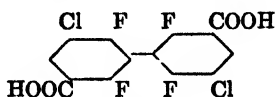
LXXXIV

2,2',6,6'-Tetrafluoro-3,3'-
dichloro-5,5'-dicarboxydiphenyl

OCH₃ F COOH

HOOC   F   OCH₃
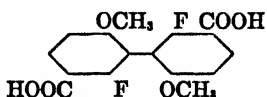
LXXXV

2,2'-Difluoro-3,3'-dicarboxy-
6,6'-dimethoxydiphenyl

_OCH₃ OCH₃ COOH

HOOC   OCH₃ OCH₃

LXXXVI

2,2',6,6'-Tetramethoxy-
3,3'-dicarboxydiphenyl

___OCH₃ OCH₃ NH₂

NH₂ OCH₃ OCH₃
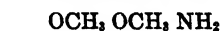
LXXXVII

2,2',6,6'-Tetramethoxy-
3,3'-diaminodiphenyl

In no instance was more than a single salt obtained and none of these showed mutarotation even at low temperatures or gave an active acid on decomposition. A possible exception was the observation of a very slight mutarotation at low temperatures in the camphor sulfonate of LXXXVII. It appears, then, that these are truly representatives of 2,2',6,6'-tetrasubstituted diphenyls in which the ortho groups do not interfere sufficiently to allow resolution.

Resolvable but easily racemized diphenyls

The preparation of analogous molecules containing one or more somewhat larger substituents followed. Stanley and Adams (158), on the basis of the interference data (table 2, p. 284), predicted the resolvability and easy racemization of LXXXVIII and of LXXXIX (161, 75). Both of these compounds were synthesized and found to racemize very easily on warming them in a

neutral solvent, and thus they stood out in sharp contrast to the stable active diphenyls studied in the earlier development of the field. Greater stability was expected in XC and actually was found.
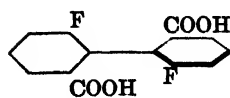
LXXXVIII
2,2'-Difluoro-6,6'-
dicarboxydiphenyl
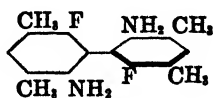
LXXXIX
2,2'-Difluoro-3,5,3',5'-
tetramethyl-6,6'-diamino-
diphenyl
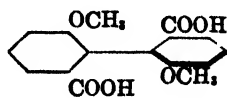
XC
2,2'-Dimethoxy-
6,6'-dicarboxy-
diphenyl

Comparison of size of ortho groups and rates of racemization

To make certain that the size was of primary importance and that no specific effect of the fluorine or methoxyl groups was involved, still larger groups along with the fluorine and methoxyl groups were introduced into the molecule. Kleiderer and Adams (76) prepared XCI and found that the active forms did not racemize. In a similar manner XCII and XCIII gave relatively stable active forms which racemized only slowly at higher temperatures (8, 185).
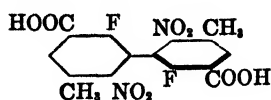
XCI
2,2'-Difluoro-3,3'-dicarboxy-
5,5'-dimethyl-6,6'-
dinitrodiphenyl
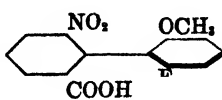
XCII
2-Nitro-6-carboxy-
2'-fluoro-6'-
methoxydiphenyl
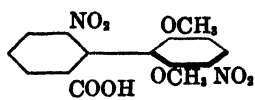
XCIII
2-Nitro-6-carboxy-
2'-fluoro-6'-
methoxydiphenyl

Although the 2,2',6-trisubstituted diphenyls previously studied could be racemized at high temperatures, Stearns and Adams (163) found that the active forms of XCIV were perfectly stable to the usual means of racemization.
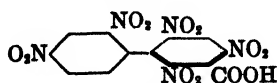
XCIV
2,4,6,2',4'-Pentanitro-
3-carboxydiphenyl

The comparison of several of these compounds is given in table 3.

By considering the last three compounds in the table, the racemization of which was carried out in the same solvent, it can be seen that the values for the relative interferences of the groups as deduced from x-ray data fit in surprisingly well with the experimental data on the rates of racemization.

TABLE 3

Rates of racemization and interference values of four diphenyls

GROUPS AT 2,2′ 6,6′	INTER-FERENCE OVER 2 90 Å.	REPRESENTATIVE COMPOUND	ANTIPODAL STABILITY
F, COOH	0.05		Complete racemization after 10 minutes boiling in acetic anhydride.
F, NH₂	0.05		Complete racemization after 30 minutes boiling in acetic acid.
OCH₃, COOH	0.11		Half-life period 78 minutes in boiling glacial acetic acid.
F, NO₂	0.41		No racemization in boiling acid, alkaline, or neutral solution

(B). A direct comparison of the effect of different groups might be obtained if the racemization rates of a series of 2,2′,6,6′-tetrasubstituted diphenyls were studied in which merely the group in one position only was modified from member to member of the series. To obtain such compounds, however, is extremely difficult, since it is necessary as well that the other groups present

be of such a character that the resulting compounds are more or less readily racemized. Such conditions are more readily obtainable in the 2,2′,6-trisubstituted diphenyls and the synthesis of the proper compounds is more feasible. Adams and his students investigated various compounds in this group. They (57, 166) selected for study the two following sets of compounds: (a) 2-x-2′-nitro-6′-carboxydiphenyl (XCV), where x = methoxyl, methyl, carboxyl, or nitro, and (b) 2-y-5-methyl-2′-nitro-6-carboxydiphenyl (XCVI), where y = fluorine, chlorine, or bromine.

Series a   Series b

XCV   XCVI
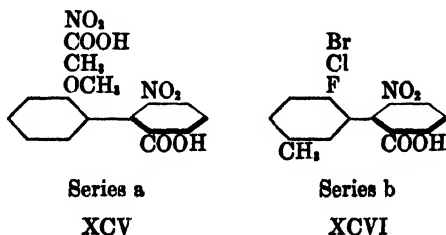
In this connection it may be pointed out that Kuhn and Albrecht (83, 84) demonstrated that the decrease in optical activity of diphenyls obeyed the law of a first order reaction and expressed the rate of racemization in terms of half-life periods.[16] This furnished at least a convenient semi-quantitative measure of stability of such compounds under different conditions, and was adopted in the discussion of the series of compounds with varying rates of racemization.

The presence of the 5′-methyl group in Series b, as will be discussed in a later chapter, probably had very little effect upon

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[16] From the rotation values at different time intervals, the constant K of the rate of racemization can be calculated by the formula

$$K = \frac{1}{t} \log \frac{\alpha_0}{\alpha_t}$$

where t is the time in minutes, α_0 the initial rotation, α_t the rotation at time t. The half-life period is calculated from the equation

$$T = \frac{1}{K} \log 2$$

the racemization rates and, therefore, a direct comparison of the compounds in Series a and Series b was permissible.

The methoxyl and the fluorine derivatives showed an interesting phenomenon. Only one alkaloidal salt could be isolated in each instance. The brucine salt of the 2-nitro-6-carboxy-2'-methoxy-diphenyl (XCV) mutarotated in solution at room temperature and the mutarotation undoubtedly was due to the racemization of the acid portion in the salt. The active acid obtained from the brucine salt racemized rapidly at room temperature.

The brucine or quinine salt of 2-nitro-6-carboxy-2'-fluoro-5'-

TABLE 4

Comparison of rates of racemization and the relative interference values from the x-ray data

SUBSTITUTED 2-NITRO-6-CARBOXYDIPHENYL	SOLVENT	TEMPERATURE	HALF-LIFE PERIOD	AVERAGE INTERFERENCE ON EACH SIDE Å.
		degrees C.	*minutes*	
2'-Br, 5'-CH₃	Acetic acid	118	3240	0.36
2'-CH₃	Acetic acid	118	179	0.18
2'-Cl, 5'-CH₃	Acetic acid	118	154	0.26
2'-NO₂	Acetic acid	118	125	0.27
2'-COOH	Acetic acid	118	91	0.09
2'-OCH₃	Absolute alcohol	25	9.4	0.04
2'-F, 5'-CH₃	No active acid obtained			0.01

methoxydiphenyl (XCVI) showed no mutarotation at room temperature but did show it at 0°C.; an equilibrium value resulted at that temperature identical with that obtained by dissolving the salt at room temperature and cooling to 0°C. At room temperature the mutarotation was obviously so rapid that it could not be followed experimentally. The acid from this salt certainly would be extremely sensitive to racemization and in spite of all precautions, no active acid could be obtained by decomposition of the salt even at −5°C.

The other five compounds had normal properties. Both salts were isolated and both active forms of each compound were obtained. The active acids could be racemized only at higher

temperatures. The rates of racemization are given in table 4, with the estimated interference values (158) for comparison.

From the half-life periods it appeared that the relative interference effects of the seven groups studied would be in the following order—Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F. Racemization tests in other solvents showed practically the same order. It is noticeable how closely the order followed that of the calculated interference values. The discrepancy between half-life periods and calculated interferences of the nitro and methyl or chlorine groups probably may be attributed to an error in the estimation of the internuclear distance to the center of the methyl group, since many experiments have indicated the methyl as larger than the other two. Moreover, there was always a certain experimental error in the determination of the half-life periods.

2,2'-Disubstituted diphenyls

(C). The possibility of optically active 2,2'-disubstituted diphenyls is of particular interest, because several investigators simultaneously directed their attention to the solution of this problem. After the resolution of 2,2'-dinitro-6,6'-dicarboxydiphenyl, several attempts to resolve 2,2'-disubstituted compounds were made without success (see Section IV).

Bell and Robinson (14) pointed out the theoretical possibility of resolution of 2,2'-disubstituted diphenyls as a logical consequence of the obstacle theory. Suitable derivatives for testing this point were not obtained however. Stanley and Adams (160) were unable to resolve XCVII which, from the standpoint of estimated interferences, offered some possibility of resolution. The compound yielded very insoluble alkaloidal salts which were impossible to fractionate and which gave no active acid on decomposition; moreover, the dimenthyl ester could not be fractionated into stereoisomers. From x-ray experimentation it is known that the carbon–sulfur distance is large and Stanley and Adams (159) consequently attempted the resolution of XCVIII. Owing to the procedure followed in attempts at resolution, they obtained and reported negative results.
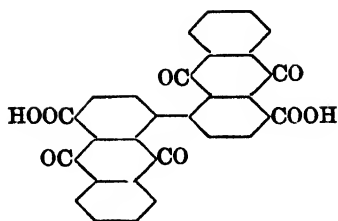
XCVII

4,4'-Dicarboxy-1,1'-
dianthraquinonyl
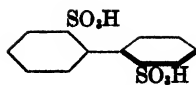
XCVIII

Diphenyl-2,2'-
disulfonic acid

Shortly after, the successful resolution of XCIX was published independently by Stanley (156), by Corbellini (47), and by Meisenheimer and Beisswenger (120). This compound could
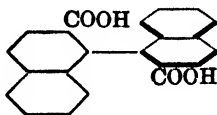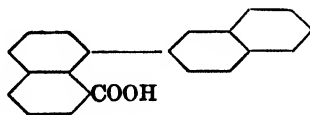

LXVII

2,2'-Dicarboxy-
1,1'-dinaphthyl
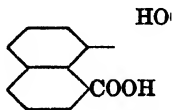
XCIX

8,8'-Dicarboxy-
1,1'-dinaphthyl
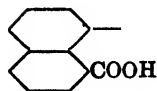
C

-Carboxy-1,1'-dinaphthyl

CI

8-Carboxy-1,2'-dinaphthyl

be considered as a disubstituted diphenyl with two C—COOH groups in the 2 and 2' positions. The existence of optical isomers indicated that these groups were sufficiently large to interfere with the hydrogen atoms even though the active acids were readily racemized. The instability of this active compound as compared with that of its very stable isomer (LXVII) was striking.

Meisenheimer and Beisswenger (120) also described the preparation and resolution of C. Its active forms were less stable than those of XCIX. A third compound, CI, was found nonresolva-

ble and it appeared that with only one substitution the molecule was much more mobile.

Since there is a difference between derivatives of 1,1'-dinaphthyl and those of diphenyl, in that the groups attached to the 8 and 8' positions in the dinaphthyl have a spatial orientation which cannot be reproduced in the diphenyl series, the results are not directly comparable with those in the diphenyl series. Nevertheless, the results offered a further indication that 2,2'-disubstituted diphenyls with proper groups should be resolvable. Lesslie and Turner (104) reported the optical resolution of CII.
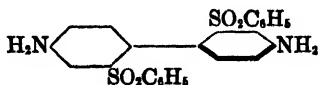
CII

Diphenyl ester of 4,4'-diamino-diphenyl-2,2'-disulfonic acid
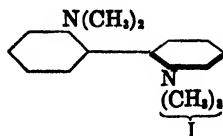
CIII

Monomethiodide of 2,2'-*bis*-(dimethylamino)-diphenyl

Moreover, these same investigators (105) resolved diphenyl-2,2'-disulfonic acid (XCVIII) a compound which Stanley and Adams (159) predicted might resolve but which they failed to obtain in active forms because of the method employed in attempting resolution. Turner (177) also separated CIII into active components. The cold aqueous solution of the active forms in which the ionization was practically complete, retained its activity for indefinite periods. Turner considered that the asymmetry of the molecule was due to the dynamic effect of the two methyl groups attached to the nitrogen atoms.

Corbellini (48) obtained a mutarotating salt from CIIIa, and also from the corresponding compound having two methyls in place of the phenyls attached to the carbon holding the hydroxyl group (48a). Stanley and Adams (159) predicted the resolvability of derivatives of 2,2'-diiododiphenyl and possibly of 2,2'-dibromodiphenyl. This prediction was realized when Searle and Adams (142, 143) were able to separate CIV into enantiomorphs and to obtain mutarotation in the salt of CV.
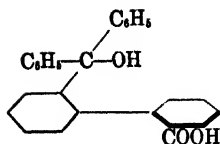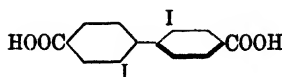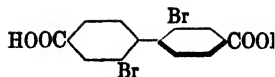
| CIIIa	CIV	CV
2-(Diphenylhydroxy-methyl)-2'-carboxy-diphenyl	2,2'-Diiodo-4,4'-dicarboxydiphenyl	2,2'-Dibromo-4,4'-dicarboxydiphenyl

Steric effects of nuclei combined to the atom attached to the ring

(D). The steric effect of the hydrogens in the hydroxyl, the amino, or the methyl groups might be expected to be appreciable. Moreover, such an effect would be greater, probably, in the methyl than in the amino, and, in turn, greater in the amino than in the hydroxyl group. An estimate of these interferences was made in the calculation of the internuclear distances by Stanley and Adams. Such influences undoubtedly would vary widely though, in general, probably would be small on account of the free rotation existing between the atom holding the hydrogens and the carbon atom of the ring to which it is attached. With larger nuclei combined to the atom attached to the ring, greater influences might be exerted, depending upon the sphere of influence and character of the atoms present.

No systematic study along these lines has been, as yet, completed. An indication of what may be expected can be seen in a comparison of the racemization rates of the active acid, ester, and amide of 2,2'-dimethoxy-6,6'-dicarboxydiphenyl (CVI) (161). In glacial acetic acid the half-life periods of the acid, ester, and amide were 78, 88, and 240 minutes, respectively. The amino in the —$CONH_2$ group was sterically much more effective than the hydroxyl or the ethoxyl.
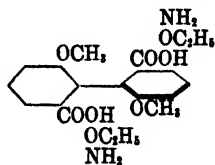
CVI

2,2'-Dimethoxy-6,6'-dicarboxydiphenyl and derivatives

All these experimental results favor the obstacle theory. Some confusion regarding the interpretation of the theory appears to exist, since Bergmann (16) suggested the obstacle theory as unnecessary and yet considered the "mutual influence of the electron shells of the atoms or groups" to be the chief consideration, and Bretscher and Wolf (24) expressed a similar view. Their conception, however, is similar to that of other previous investigators in the field (159) who have used the term "obstacle."

An occasional objection is raised to the obstacle theory. Turner (175) argued that if steric effects were large, it would be expected that 2-nitrodiphenyl would nitrate to a larger extent in position 4′ and less in position 2′, than would 4-nitrodiphenyl. Actually it was found that 2-nitrodiphenyl nitrated 39 per cent in position 2′, and 4-nitrodiphenyl only 37 per cent in this position. Turner considered this as evidence that steric effects of one group were not of first importance. But in this case the steric effects would appear to be of somewhat different character and the value of this conclusion is dubious.

Electrical effects of groups

The experimental evidence in this last section has been discussed merely from the standpoint of the size of the atoms or groups. What is the evidence in regard to the electrical effects of the groups? In attempting to answer this question it is pertinent to consider diphenyls in which all four ortho groups are identical. The diphenyl molecules containing four methyls, four chlorines, four nitros, four methoxyls, and four fluorines in the ortho position, have been studied from the standpoint of resolution, and when resolved, their racemization rates have been determined. The compounds containing the four chlorines and four nitro groups which are polar in character were very resistant to racemization. But the compound with four methyl groups, which are essentially nonpolar and approximately the same size as the chlorines, was also very resistant to racemization. On the other hand, the tetrafluoro and tetramethoxy compounds were neither of them even resolvable. In fact, by considering all of the large variety of compounds already studied, it is impossible to correlate electrical characteristics and interference effects of

the individual groups. Steric influences due to the polarity of groups probably produce no more than a secondary effect.

VIII. EFFECT OF FACTORS OTHER THAN THE SIZE OF ORTHO GROUPS

The foregoing experimental facts present a preponderance of evidence that the size of ortho groups is a major factor in the resolvability or nonresolvability of certain diphenyl compounds and in the stability of the active molecules. But in such a complex molecule as a substituted diphenyl, it is not surprising that other factors exist which may affect more or less the stability of the active isomers.

Substituents in positions other than the 2,2',6,6' positions

It was first noted by Kuhn and Albrecht (84) that the half-life period of active CVII in 2 N sodium hydroxide solution at 98°C. was eighteen minutes, and that of CVIII, under the same conditions, was fifty minutes. Thus antipodally the latter was three times as stable as the former. This was inexplicable if the 2,2', 6,6' groups were the only factors which affected the stability to racemization of the active molecules.
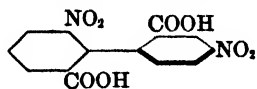

CVII	CVIII
2,4'-Dinitro-2',6'-dicarboxydiphenyl	2,4,4'-Trinitro-6,6'-dicarboxydiphenyl
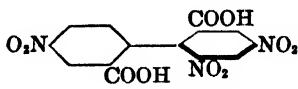
Later, Adams and his students started a systematic study on this particular phase of the diphenyl stereochemistry. Yuan and Adams (194, 195) prepared a series of compounds, each of which was a 5'-substituted 2-nitro-6-carboxy-2'-methoxydiphenyl with the 5' group successively methoxyl, methyl, chloro, bromo, and nitro (CIX). These were compared with the unsubstituted
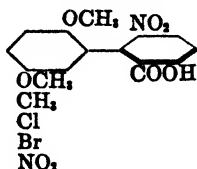
CIX

2-nitro-6-carboxy-2'-methoxydiphenyl which racemized readily at room temperature and thus made possible a fairly accurate polariscopic study of the rate of racemization. The determination of the effect of each of a variety of groups in the 5' position was thus possible. For each compound merely one alkaloidal salt could be isolated and all of these mutarotated in solution. The active acids obtained from the salts racemized readily in organic solvents at room temperature. The half-life periods of the various molecules varied from compound to compound (table 5). A comparison of the rates of racemization of the free acids indicated that the stabilities of the unsubstituted, the 5'-methoxyl

TABLE 5

Half-life periods at 26°C. of the active forms of substituted 2-nitro-6-carboxy-2'-methoxydiphenyls and their salts

COMPOUND	HALF-LIFE PERIOD IN MINUTES	
	Free acid in alcohol	Brucine salt in chloroform
	minutes	*minutes*
No substituent	9.4	12.0
5'-OCH₃	10.8	16.7
5'-CH₃	11.5	15.8
5'-Cl	31.0	16.7
5'-Br	32 0	16.7
5'-NO₂	35.4	7.7

and the 5'-methyl derivatives were practically the same, the stabilities of the 5'-chloro and 5'-bromo were also identical and more stable than the first three. The 5'-nitro appeared to be somewhat more stable than the 5'-halogen derivatives.

Only a few results on analogous compounds (58) with substituents in the 4' and 3' positions are as yet available, but it is clear that the effect of groups in these positions will be different from that in the 5' position. The 4'-nitro (CX) racemized less readily than the corresponding 5' derivative, and the 4'-methoxyl (CX) more readily than the corresponding 5' derivative. The 3'-methyl (CXI) homolog (38) unlike the 5' derivative could not be obtained in active forms nor did the alkaloidal salts mutarotate.

CX   CXI
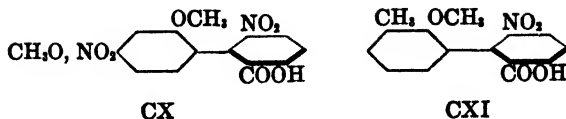
From these data it becomes obvious that groups other than the 2,2',6,6' do affect the stereoisomeric stability of the active diphenyl compounds. The theoretical basis for and the exact mechanism of this phenomenon are still obscure, but it may involve one or more, or possibly all, of the following causes (195). (1) The variation of the valency angle at which the ortho substituent on the ring is attached, thus changing the effective size of the group; (2) the slowing down of the semicircular oscillation of the two phenyl rings by substituents, thus diminishing the chances of the complete rotation; (3) the modification of the distance between 1,1' carbon atoms with the nature of substituents; (4) the bending of the linkage between the two rings in such a way that the rings are no longer coaxial. There appears also to be some parallelism between the rates of racemization of these diphenyls and the dipole moments of the corresponding substituted anisoles, which comprise half of the respective molecules. The experimental results are perhaps significant in leading to the conclusion that cause 2 is not a factor, since the substitution of two atoms of similar polarity but of different weight, such as chlorine and bromine, resulted in essentially identical effects on the rate of racemization.

Comparison of isomeric 2,2',6-trisubstituted compounds

Another interesting comparison is that of the stability of three 2,2',6-trisubstituted diphenyls where the groups are the same but differ in their relative positions. If the two rings remain symmetrically placed as they approach the same plane, the rate of racemization would be determined by the ease with which the group of position 2' could pass the smaller or less interfering of the groups at positions 2 and 6. Thus, in CXII, where R_3 is the largest group, R_2 the next in size, and R_1 the smallest or least interfering group, the rate of racemization would depend chiefly on the ability of the group R_1 to pass the group R_2. The passing

of the groups R_1 and R_2 would be more difficult, so would have less effect on the rate of racemization.

CXII CXIII CXIV
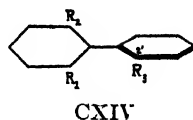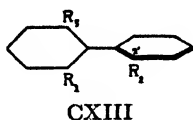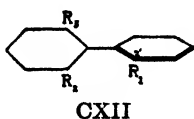
In compound CXIII, where the groups have been interchanged, the ability of the groups R_1 and R_2 to pass each other would again be the largest factor determining its rate of racemization. These two compounds then would be expected to racemize at about the same rate.

A third interchange of groups resulting in compound CXIV should produce a more stable system than either of the above two, because here the group R_1 would have to pass the largest group R_2 in order for the compound to racemize.

On the other hand, if the molecule is mobile, then an average interference is the significant factor, and the rate of racemization of each should be approximately the same.
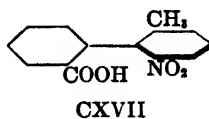
Actually, three substituted diphenyls illustrating the above types were prepared and studied (57, 165). They were CXV, CXVI, and CXVII.
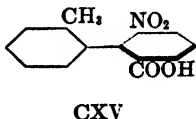
CXV CXVI CXVII
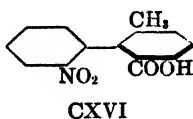
2-Nitro-6-carboxy-2'-   2-Methyl-6-carboxy-   2-Methyl-6-nitro-
methyldiphenyl   2'-nitrodiphenyl   2'-carboxydiphenyl

Since the methyl was the largest group as determined by racemization values, compounds CXV and CXVI should be of about the same stability, and compound CXVII should be less stable. Experimentally, it was found that compound CXV racemized most readily, CXVI the next, and CXVII the least readily of all. The interchange of ortho substituents must, therefore, involve certain relative influence factors which affect the stability of the active molecules.

It is desirable here to point out other unexpected phenomena which must be attributed to some factors in the molecule other than the size of ortho groups. The mutarotation of the salts of the series of acids previously mentioned in which a variable 5' group was involved, did not run parallel to the rates of racemization of the acids. The sodium salts of many optically active diphenyl derivatives racemized in aqueous solution more readily than the free acid racemized in organic solvents. This was assumed to be due, possibly, to ionization and the smaller size of the COO⁻ group. It was found, however, that the sodium salts of all the substituted 2-nitro-6-carboxy-2'-methoxydiphenyls in water racemized less readily than the free acids in organic solvents (195). The sodium salts in absolute alcohol, however, racemized more readily than the free acids in the same solvent.

It might appear at first from the relatively large change in the racemization rates caused by substituents in positions other than the 2,2',6,6', that such substituents play a very important rôle. Nevertheless, it must be considered that the amount of change is something about which no quantitative information is available. It is quite possible that small changes in interference have a large observed effect, particularly on those molecules which are sensitive to racemization under mild conditions.

So far the experimental data are not sufficient to give a clue as to the nature of these phenomena.

IX. POLYPHENYL SYSTEMS

Compounds having more than one asymmetric carbon atom possess a number of diastereoisomers, and the same phenomenon is to be expected in derivatives of properly substituted polyphenyls containing several asymmetric centers. The stereoisomerism of p-diphenylbenzenes was first discussed by Stanley and Adams (157, 78).
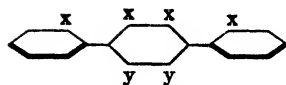
Theoretically, there are four general types of properly substituted p-diphenylbenzenes.
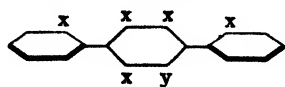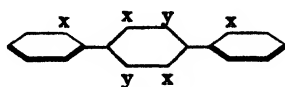
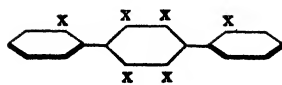Type 1   Type 2

Type 3   Type 4

Type 1 contains two dissimilar asymmetric centers and should, therefore, exist in two disastereoisomeric forms, each of which is a racemic modification, one *cis* and one *trans*. Compounds of Types 2 and 3 have two similar asymmetric centers and, therefore, should exist in two forms, one meso and one racemic. The meso form of Type 2 is the *trans* form, and the racemic is the *cis* form. On the other hand, the meso form of Type 3 is the *cis* form, and the racemic is the *trans* form. It is of interest that the meso form of Type 2 has not the usual plane of symmetry, but a point of symmetry. In Type 4 the central ring is symmetrically substituted so that there exist no asymmetric centers and consequently no optical isomerism is possible. On the other hand, restricted rotation is still capable of existence and two geometric isomers, *cis* and *trans* forms, result.

Properly substituted *meta-* and *ortho-* diphenylbenzene derivatives yield analogous, though somewhat different, types of stereoisomers. Type 5, with two different asymmetric centers, should exist in two diastereoisomeric racemic forms, one *cis* and the other *trans*. In Type 6 the two asymmetric centers are identical, so that meso and racemic modifications exist. As a plane of symmetry is present in the *cis* modification, it will be the meso, and the *trans* modification will be the racemic. Such a compound corresponds to Type 3 of the *p*-diphenylbenzene series. Similar conditions obtain in Type 7, in which a single group in the central ring acts as an interfering group for both asymmetric centers.
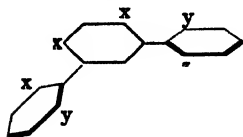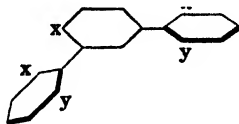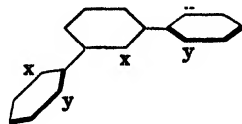
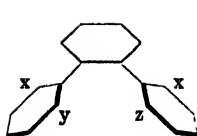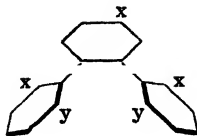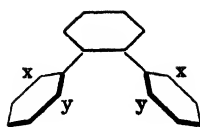Type 5   Type 6   Type 7

In the *o*-diphenylbenzenes three types exist, as shown by Types 8, 9, and 10; it will be observed that two of these, 8 and 10, contain no substitution in the central ring. Such substitution is

Type 8   Type 9   Type 10

unnecessary for restricted rotation because of the fact that one of the terminal benzene rings acts as the third substituent to produce restricted rotation between the other terminal ring and the central ring. Only if it is desired to render the central ring unsymmetrically substituted when the two terminal rings are identical (9) is substitution necessary. Types 8 and 9 correspond to Type 5, in that two racemic modifications are possible, one *cis* and one *trans*. In Type 10 there are the meso or *cis* form and the racemic or *trans* form.

But if a model of *o*-diphenylbenzene (11) is constructed with all the rings coplanar, it can be seen that the distance 'd' between the ortho carbons in the two terminal rings is the same as that of an internuclear C—C bond, 1.45Å. Thus, merely two hydrogen substituents should collide and isomers should exist provided that the terminal rings are unsymmetrically substituted. There are then three possibilities, represented by Types 12, 13, and 14.
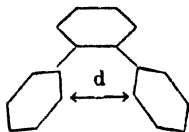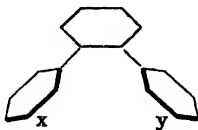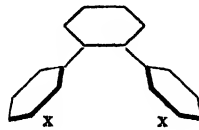
Type 11   Type 12   Type 13

Type 14

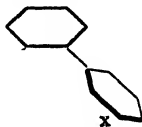In Types 12 and 13 two racemic modifications should exist, one *cis* and one *trans*; in Type 14 one racemic, the *trans* form, and one meso, the *cis* form. Such isomers as have just been pictured are dependent on the assumption that the oscillation of the two terminal rings is not synchronized in such a way as to prevent collisions.

Properly substituted polyphenyls with more than three nuclei will involve more than two asymmetric centers and, therefore, will make possible the existence of additional stereoisomers. By way of illustration may be cited one general case in which three asymmetric centers are present.
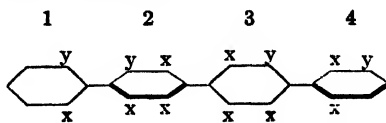
A quaterphenyl of this type should occur in four racemic modifications where the possible configurations of the pairs of rings are as follows:

Rings	
1,3	2,4
cis	cis
cis	trans
trans	cis
trans	trans

The special cases in the polyphenyls are even more numerous.

Experimentally, only p-diphenylbenzene derivatives have as yet been investigated. The possibility for the existence of a meso and a racemic modification of substituted p-diphenyl-benzenes of Type 2 was demonstrated by the isolation (25) of two stereoisomeric compounds, CXIX and CXX, prepared by bro-nination of CXVIII, a product from the reaction of m-xylene, quinone, and aluminum chloride. Each of the two isomers formed individual series of derivatives but oxidized to the same quinone CXXI. The quinone, in turn, upon reduction always gave a mixture of the two hydroquinones, CXIX and CXX.

Sufficient interference apparently was not present in the qui-none to allow the existence of two isomers. From the quinone by treatment with alkali (53), a dihydroxyquinone (CXXII) was formed which, on acetylation and reduction, gave a diacetoxy-hydroquinone (CXXIII) which, on acetylation, gave a tetraace-tate (CXXIV). This last compound belongs to Type 4 and should occur in cis and trans modifications. Only one form was obtained, but from the available knowledge that the hydroxyl group or its derivatives had only a very small interfering effect, this was not an unexpected result.

CXVIII

3,6-Di-(2,4-dimethylphenyl)-
hydroquinone

CXIX

trans-3,6-Di-(2,4-dimethylphenyl)-
2,5-dibromohydroquinone

CXX

cis-3,6-Di-(2,4-dimethylphenyl)-
2,5-dibromohydroquinone

CXXI

3,6-Di-(2.4-dimethylphenyl)-
2,5-dibromobenzoquinone

CXXII

3,6-Di-(2,4-dimethylphenyl)-
2,5-dihydroxybenzoquinone

CXXIII

3,6-Di-(2,4-dimethylphenyl)-
2,5-diacetoxyhydroquinone

CXXIV

3,6-Di-(2,4-dimethylphenyl)-
1,2,4,5-tetraacetoxybenzene

A second compound (148, 149) in which all of the ortho positions were filled furnished a more suitable compound for testing the validity of the predictions. By brominating CXXV, a product from the reaction of mesitylene, quinone, and aluminum chloride, two stereoisomeric compounds CXXVI and CXXVII were formed. These isomers were converted readily to characteristic derivatives. Upon bromination they produced the same

hexabromo derivative (CXXVIII), thus experimentally confirming the fact that stereoisomers exist only if each of the rings is unsymmetrically substituted.

Each of the two tetrabromodimesitylhydroquinones, CXXVI and CXXVII, unlike the two dibromodixylylhydroquinones, CXIX and CXX, which oxidized to the same quinone, yielded, upon oxidation, the stereoisomeric quinones (CXXIX and CXXX). The additional *o*-methyl group increased the interference sufficiently to produce restricted rotation and thus allowed the formation of isomers in the quinones. Incidentally, these quinones present an example of restricted rotation between a benzene and a quinone ring, the first instance of such isomerism to be found in systems other than diphenyl.

CXXV
3,6-Di-(2,4,6-trimethylphenyl)-
hydroquinone

α-form-meso-*trans*

CXXVI
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromohydroquinone

β-form-racemic-*cis*

CXXVII
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromohydroquinone

CXXIX
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromobenzoquinone

CXXX
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromobenzoquinone

CXXVIII
3,6-Di-(3,5-dibromo-2,4,6-trimethyl-
phenyl)-2,5-dibromohydroquinone

The two diastereoisomeric dibromoquinones (CXXIX and CXXX) with aqueous sodium hydroxide were converted to two stereoisomeric dihydroxyquinones (CXXXI and CXXXII) (149).
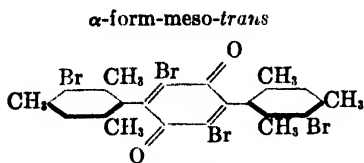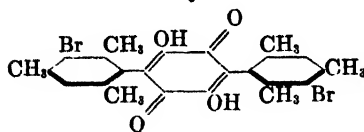
α-form-meso-*trans*   β-form-racemic-*cis*

CXXIX   CXXX

↓   ↓
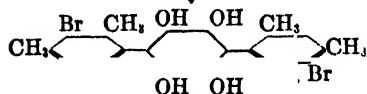
CXXXI   CXXXII
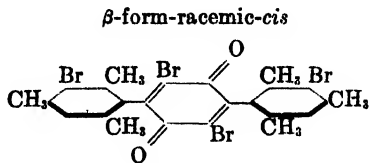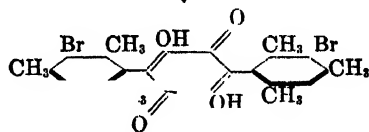
3,6-Di-(3-bromo-2,4,6-trimethyl-   3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dihydroxybenzoquinone   phenyl)-2,5-dihydroxybenzoquinone

↓   ↓
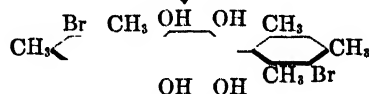
CXXXIII   CXXXIV

3,6-Di-(3-bromo-2,4,6-trimethyl-   3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-1,2,4,5-tetrahydroxybenzene   phenyl)-1,2,4,5-tetrahydroxybenzene

Each of these two latter compounds formed the expected individual series of derivatives,—namely, the diacetoxyquinones, the dibutyroxyquinones, the diacetoxyhydroquinones, the tetrahydroxy compounds (CXXXIII and CXXXIV), the tetraacetoxy and tetrabutyroxy compounds. The last three pairs belonged to the p-diphenylbenzenes of Type 4 and represented *cis* and *trans* isomers incapable of optical isomerism. On the other hand, the two hydroxyquinones and their derivatives represented pairs of *cis* and *trans* isomers, in each pair of which one is a meso and one a racemic modification.

Owing to the small size of the hydroxyl group, the *cis* form of the dihydroxyquinone (CXXXII) and its diacetate and dibutyrate could be converted, by heating in high-boiling solvents,

into the corresponding *trans* forms. Similar treatment did not cause the conversion of any of the other *cis* forms in this series.

The high-melting forms in the dimesitylbenzene and dimesitylquinone series were assumed by analogy to other known pairs of stereoisomers to be the *trans* modifications, and the low-melting forms to be the *cis* modifications. That this assumption is correct Shildneck and Adams (150) proved experimentally by the isolation of two diastereoisomeric menthoxyacetates (CXXXV and CXXXVI) of the *cis* form and only one such derivative of the *trans* form.
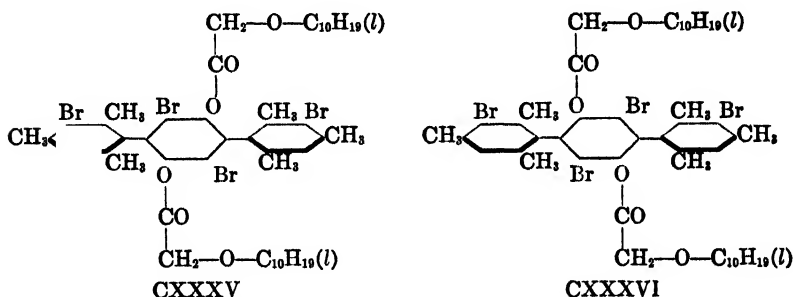
CXXXV   CXXXVI

3,6-Di-(3-bromo-2,4,6-trimethylphenyl)-
2,5-dibromohydroquinone dimenthoxyacetate

From the two compounds CXXXV and CXXXVI, the two active forms of the dihydroxy compound (CXXVI) were obtained by hydrolysis.

From these results, though limited in number, it is obvious that in the diphenylbenzene system the exact conditions hold that would be expected from the study of the diphenyl series.

X. EXTENSION INTO NONBENZENOID RING COMPOUNDS

The search for the presence of stereoisomerism in certain substituted molecules containing rings of an aromatic but nonbenzenoid type is a natural development from the study of diphenyl compounds. Such a field includes compounds in the series of the phenylpyridines, dipyridyls, phenylpyrroles, dipyrryls, phenylpyrazoles, etc. The difficulty of synthesis, however, is a severe hindrance to the rapid development of the study of these types.

Apparently the first suggestion that the stereoisomerism ob-

served in the diphenyl series might also occur among binuclear heterocyclic substances is due to Kermack and Slater (73), who attempted the resolution of CXXXVII but met with failure.

CXXXVII
3-(o-Nitrophenyl)-indole-
2-carboxylic acid

CXXXVIII
2-(o-Carboxyphenyl)-3-carboxy-
pyridine methylsulfate
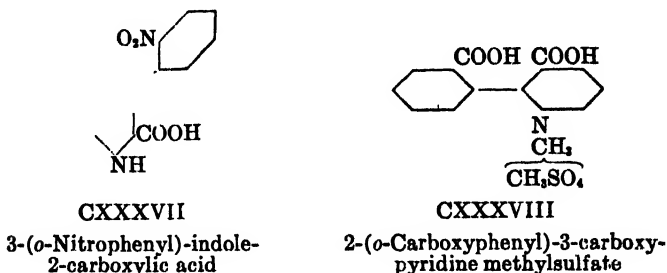
Lions and his coworkers (35, 109) made attempts to provide a blocking group in the 2-phenylpyridine series by conversion of the tertiary nitrogen atom into a quaternary salt. Thus CXXXVIII was examined, but its resolution was not effected.

Steele and Adams (164) prepared two substituted phenyl-pyridines, CXXXIX and CXL, but were unable to resolve them.

CXXXIX
2-(2-Carboxy-6-chlorophenyl)-
3-carboxypyridine

CXL
3-(2-Carboxyphenyl)-2,4-
dicarboxy-6-phenylpyridine
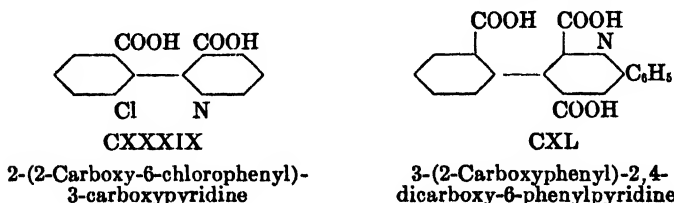
The negative results were attributed to possible distortion within the molecule with subsequent free rotation, due, possibly, to the character of the pyridine ring or to the electrical attraction of the basic nitrogen and acid carboxyl groups which would disturb the normal interferences.

Phenylquinones, phenylpyrroles, dipyrryls, dipyridyls

In the study of terphenyl derivatives (148) two stereoisomeric diphenylquinones (CXXIX and CXXX) were obtained, and as mentioned previously these compounds represented the first examples of a diphenyl type of isomerism in compounds which have one of the rings not a benzene nucleus.

Later, Hill and Adams (60) prepared and resolved CXLI into optical enantiomorphs. Another substituted phenylquinone (CXLII) of the resolvable type (196) was prepared, but resolution was not effected because attempts to introduce proper salt-forming groups into the molecule resulted in failure.
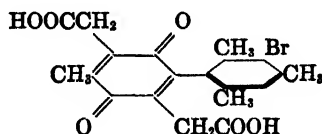
CXLI

2-(3-Bromo-2,4,6-trimethylphenyl)-
5-methylbenzoquinone-3,6-di-
(acetic acid)
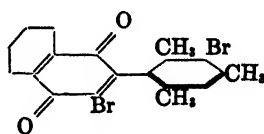
CXLII

2-(3-Bromo-2,4,6-trimethylphenyl)-
3-bromo-1,4-naphthoquinone

In spite of the fact that several attempts to resolve a C—C linked phenylpyridine were unsuccessful, the resolution of a 2,2′,6,6′-substituted dipyridyl into optically active isomers was reported by Woodruff and Adams (193). Upon oxidation of phenanthroline with potassium permanganate, CXLIII was obtained and resolved. The active acids were readily racemized by warming for a short time in ethyl alcohol.
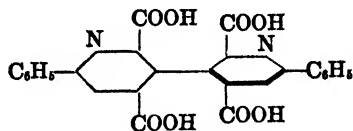
CXLIII

2,4,2′,4′-tetracarboxy-
6,6′-diphenyl-3,3′-di-
pyridyl

Perhaps the most fruitful and interesting results in the field of binuclear compounds other than diphenyls was obtained from the study of compounds of N-phenylpyrrole and N,N'-dipyrryl types. Different from all the compounds previously studied where the attachment of one ring to the other is through carbon linkages, substituted N-phenylpyrroles represent a class of bicyclic compounds with carbon–nitrogen linkages between the rings.

Bock and Adams (19) prepared and resolved CXLIV. The active forms were exceedingly stable and did not racemize upon boiling for eight hours in ethyl alcohol, and were only completely racemized by boiling for twenty-four hours in 0.1 N sodium hydroxide solution. Then a dipyrryl (CXLV) was resolved by Chang and Adams (37) and the active forms were found to be unusually resistant to racemization.
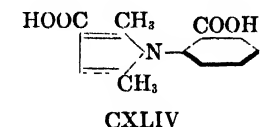
CXLIV

N-2-carboxyphenyl-2,5-
dimethyl-3-carboxypyrrole

CXLV
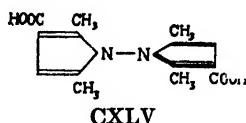
N,N'-2,5,2',5'-tetramethyl-
3,3'-dicarboxydipyrryl

If the usual explanation of the phenomenon in the diphenyl series is applied here, it may be said that there is restricted rotation between the benzene ring and the pyrrole ring or between the two pyrrole rings, owing to the interference of the ortho groups. In this case, the three valences of each nitrogen must be assumed to be in a single plane or at least to oscillate through a configuration in which the two rings are coaxial. With these assumptions, more or less the same conditions should hold for optical isomerism in phenylpyrroles as in the diphenyl series, namely, two or more groups of proper size substituted in the ortho positions and unsymmetrical substitution in each of the rings. Experimental facts have conformed to this view.

Bock and Adams (20) were unable to resolve any of the following compounds—CXLVI, CXLVII, and CXLVIII. These represent two examples of o-disubstitution and one of symmetry in one ring.
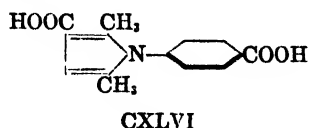
CXLVI

N-(4-carboxyphenyl)-
2,5-dimethyl-3-carboxy-
pyrrole
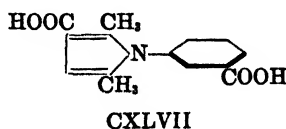
CXLVII

N-(3-carboxyphenyl)-
2,5-dimethyl-3-car-
boxypyrrole
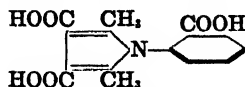
CXLVIII

N-(2-carboxyphenyl)-
2,5-dimethyl-3,4-
dicarboxypyrrole

If a fixed tetrahedral structure for nitrogen and at the same time restricted rotation are assumed, formula CXLIX would represent the appearance of such a molecule. Under these conditions unsymmetrical substitution in one ring only would be necessary to produce optical isomerism, but this does not agree with the facts (CXLVIII).
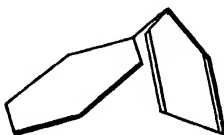
CXLIX

That optical isomerism in phenylpyrroles might be due to an asymmetric nitrogen atom is also very improbable, first because of the lack of positive results of many investigators in resolving trivalent nitrogen compounds, and second because it is difficult to see how such slight changes from formula CXLIV in the molecules CXLVI and CXLVII would eliminate optical isomerism if it were due to the nitrogen.

Analogous to *N*-phenylpyrroles are the phenylcarbazoles. Patterson and Adams (135) were unable to resolve CL which contained the symmetrical carbazole ring, but obtained optical isomers from CLI which contained the unsymmetrically substituted carbazole.
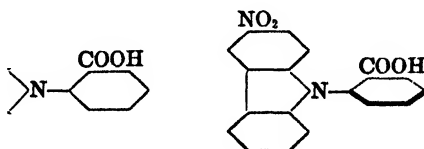
CL

N-(2-carboxyphenyl)-
carbazole

CLI

N-(2-carboxyphenyl)-
3-nitrocarbazole

Dipyrrylbenzenes

As the experimental results indicate that the isomerism is very similar to that in the diphenyl series, an extension could, therefore, be made to dipyrrylbenzenes, which should exhibit isomerism similar to that of the diphenylbenzenes. This was confirmed experimentally and it was possible to distinguish the meso and the racemic modifications by resolution studies. Chang and Adams (36) prepared the diastereoisomeric forms of the *m*-dipyrrylbenzenes (CLII). The less soluble, presumably the *trans* form, was racemic and was resolved into its highly active, stable enantiomorphs, while the more soluble, presumably *cis* form, was meso and preliminary experiments indicated that it could not be resolved. The corresponding *p*-dipyrrylbenzenes (CLIII) were also prepared, but in this case the less soluble, presumably *trans* form, is meso, and although the experimental work is still incomplete it apparently cannot be resolved, whereas the more soluble, presumably the *cis* form, is racemic and should be resolvable.
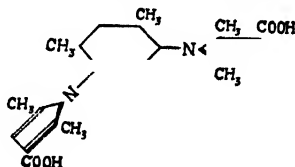
CLII
2,5-Di-*N*-(2,5-dimethyl-3-carboxypyrryl)-1,3-dimethylbenzene
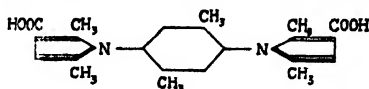
CLIII
2,6-Di-*N*-(2,5-dimethyl-3-carboxypyrryl)-1,4-dimethylbenzene

XI. FURTHER STUDIES IN RESTRICTED ROTATION

The conception of restricted rotation has been applied to the stereochemistry of molecules other than diphenyls or bicyclic compounds, and the results will be described briefly in this résumé.

Mills and Elliott (129) predicted that steric hindrance similar to that which prevents free rotation of the two nuclei in diphenyl

might be exhibited in peri-substituted naphthalenes (CLIV). They showed that the nitro derivative (CLV) could be resolved into rather easily racemized enantiomorphic forms, whereas the un-nitrated compound (CLVI) could not be. This was explained

CLIV	CLV	CLVI
	N-benzenesulfonyl-8-nitro-1-naphthyl-glycine	N-benzenesulfonyl-1-naphthylglycine
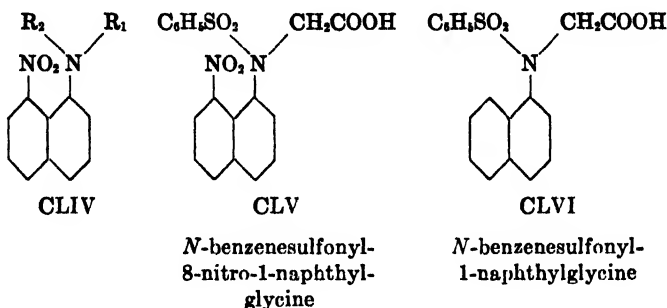
by these authors as molecular asymmetry due to restricted rotation about the C—N bond because of the collision of the R_1R_2N—group and the nitro group in the 8 position. No such obstacle existed in the un-nitrated compound (CLVI), and hence no optical activity.

A second analogous illustration of restriction was described by Mills and Breckenridge (127, 128), the resolution of CLVII in contrast to the nonresolvability of the corresponding tertiary base (CLVIII) or the corresponding 1-methylquinolinium iodide.

CLVII	CLVIII
8-Benzenesulfonylethylamino-1-ethylquinolinium iodide	8-Benzenesulfonylethylamino-quinoline
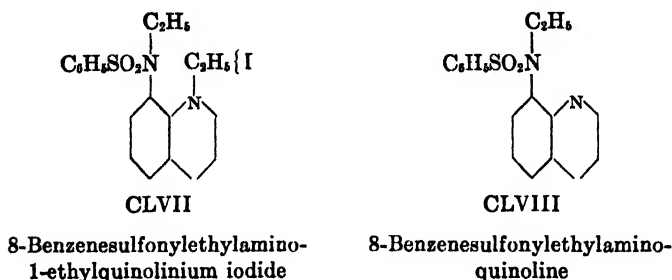
Adams and coworkers (62, 119) suggested the possibility of the resolution of other types of compounds which might be asymmetric if steric hindrance prevented free rotation. Such types are represented by the general formulas 1, 2, and 3, where R stands for groups of proper size.
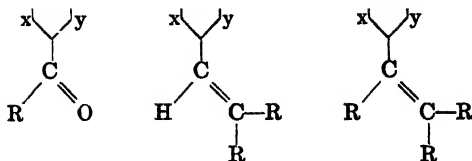
Compounds representing types 1 and 2 were prepared. They were CLIX, CLX, CLXI, CLXII, CLXIII, CLXIV, and CLXV.
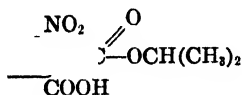
CLIX

2-Carboisopropoxy-
3-nitrobenzoic acid
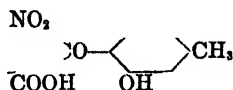
CLX

2-(2-Hydroxy-4-methylbenzoyl)-
3-nitrobenzoic acid
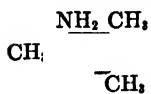
CLXI

v-Aminobenzoyl-
bromomesitylene
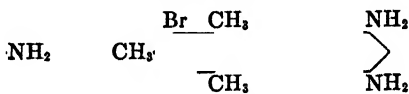
CLXII

3,5-Diaminobenzoyl-
bromomesitylene
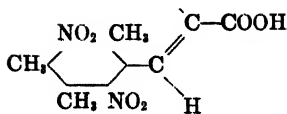
CLXIII

2,3,4,6-Tetramethyl-
2,5-dinitrocinnamic acid
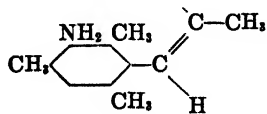
CLXIV

3-Aminoisobutenyl-
mesitylene
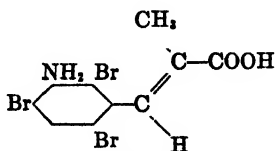
CLXV

α-Methyl-3-amino-2,4,6-
tribromocinnamic acid

In carrying out the fractional crystallization, there was no definite separation, nor did the relative size of the fractions give any indication of salts of different solubilities. In no case were optically active compounds obtained by decomposition of the salts. Substituted stilbenes were examined for optical activity by Pfeiffer and coworkers (136), but the results were all negative.

Several attempts to prepare compounds of Type 3, which showed the analogy to substituted diphenyls most completely, met with failure. The probability of isomerism of selected representatives of these compounds is supported by the more recent results of Meisenheimer upon certain oximes.

Meisenheimer, Theilacker, and Beisswenger (122) pointed out that formulas CLXVI and CLXVII represented two forms of a substituted aromatic oxime. In the molecule of the β-form of the ketoxime (CLXVII), both the hydroxyl and the R groups have the possibility of colliding with the x and y groups on the benzene ring. Thus, the rotation of the radical R—C̄=NOH would be restricted and the compound would be able to exist in antipodal forms. As for the α-form (CLXVI), there should be no interference between the hydroxyl group and the x and y groups, so that the molecule should not be resolvable.

CLXVI
α-form
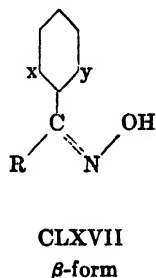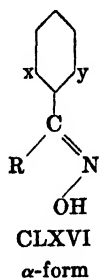
CLXVII
β-form

Experimentally, these authors found that neither form of CLXVIII could be resolved. Of the α- and β-forms of CLXIX, the α-form could not be separated into enantiomorphs. The β-oxime of the same ketone (CLXIX) yielded coniine, cinchonine, and strychnine salts, all of which exhibited mutarotation in pyridine; hence asymmetry of the molecules was inferred even

though the optically active acid could not be isolated.   The corresponding ether (CLXX), however, formed a cinchonine salt which mutarotated in solution and upon decomposition at 0°C. gave an active ether.
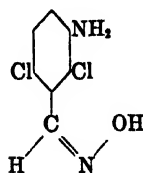
CLXVIII	CLXIX	CLXX
	(β-form)	
2,6-Dichloro-3-aminobenzaldoxime	2-Hydroxy-3-carboxy-1-naphthyl methyl ketoxime	2-Hydroxy-3-carboxy-1-naphthyl methyl ketoxime N-methyl ether
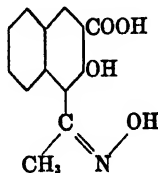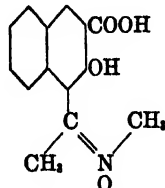
The resolution of these compounds was used as evidence for the correctness of the Hantzsch-Werner theory for the structure of oximes, and offered a new instance of optical isomerism due to restricted rotation.

The search for stereoisomerism in substituted diphenylmethane compounds was also made.   The 3,3′-diamino derivatives of dimesitylmethane (CLXXI), dimesitylsulfone (CLXXII), and dimesityl ketone (CLXXIII) were prepared and examined for optical activity by Maclean and Adams (113).   Using a similar method for calculation of interferences as in the diphenyl series, the adjacent methyl groups in CLXXI should collide, provided that the rings are coplanar and provided that the valence angles of the central carbon atom remain undistorted.
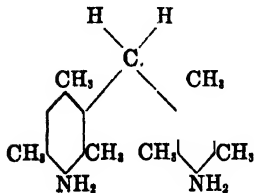
CLXXI	CLXXII	CLXXIII
3,3′-Diamino-dimesitylmethane	3,3′-Diamino-dimesitylsulfone	3,3-Diamino-dimesityl ketone

Experimentally, none of the above three compounds could be resolved. This indicates, in all probability, a distortion of the carbon tetrahedral structure or a synchronizing of the two rings during rotation.

Hayashi (59) reported the existence of two stereoisomeric benzoylbenzoic acids (CLXXIV), and discussed the possibility of the diphenyl type of isomerism. From the present knowledge of diphenyl stereochemistry, however, this explanation appears very unlikely, and it is more reasonable to suppose that the two substituted benzoylbenzoic acids are position isomers.
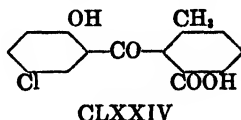
CLXXIV
2-(5-Chloro-2-hydroxybenzoyl)-
3-methylbenzoic acid

In 1907, Lees and Thorpe (93) reported isomeric N,N'-di-methyl-1,3-diamino-2-phenylnaphthalenes to which, later, Gibson and coworkers (54) assigned stereochemical formulas based on restricted rotation. Upon reinvestigation by Lesslie and Turner (101), the two compounds were shown to be position isomers.

Many substituted diphenyls have been reported by Van Alphen (184) as existing in dimorphic forms, but there appears to be no association between this phenomenon and diphenyl stereoisomerism.

XII. SUMMARY AND CONCLUSIONS

In the foregoing pages an attempt has been made to give an account of all the important investigations in the field of diphenyl stereochemistry, and it is of interest to note how an erroneous hypothesis stimulated various experimental researches and opened a new field with striking and fruitful results. Without the incentive provided by the Kaufler formula, the resolution of diphenyl compounds might not have been attempted.

The present status of the problem can be summarized in the following four points, which have been intensively studied experimentally.

(1). There is no reason to believe that diphenyl derivatives have the Kaufler folded formula.

(2). The resolution of certain substituted diphenyls and the nonresolution of others can be satisfactorily explained on the assumption that the two benzene rings in a resolvable diphenyl possess a common axis, but lie in different planes, owing to the restriction of free rotation about the axis because of the ortho substituents. The resulting configuration is asymmetric. The degree of inhibition of rotation, as manifested by the ease of racemization, depends primarily upon the size of the groups.

(3). The phenomenon persists in terphenyl compounds and binuclear compounds other than diphenyls. The restriction of free rotation about a single bond has also been found in other classes of compounds.

(4). There are factors other than the size of ortho groups affecting the optical stability of active diphenyls, but these are of lesser significance.

In concluding this résumé a brief discussion of those points upon which our knowledge is still incomplete and uncertain, may be of interest.

(1). As the accumulation of experimental information increases, the factors which influence the interfering effects of the groups appear to be numerous. The possibility of obtaining strictly quantitative information on the effect of a specified ortho substituent in any particular molecule, therefore, seems remote.

(2). It has been demonstrated experimentally that groups other than those in the $2,2',6,6'$ positions affect the rate of racemization of an active diphenyl. From the data it is impossible to distinguish whether the other groups cause (a) a variation in the size of the ortho groups per se, or (b) a change in the angle of attachment.

The trisubstituted diphenyls appear to have, in general, a greater tendency to racemize than the tetrasubstituted, even after taking into account the character and size of the ortho groups. The correct explanation of these phases of the problem is not clear.

(3). There have been two different methods suggested for

calculating the approximate interfering effects of ortho groups. Stanley and Adams (158) accepted the values of the internuclear distances as probably best representing the relative interference effects. Relative "interference values" of a pair of groups were obtained by comparing the sum of the two internuclear distances of the 2,2'-substituted groups with the known vertical distance between the 2,2' carbon atoms, 2.90Å. Lesslie and Turner (104) preferred to predict the resolvability by using the values of the atomic radii of the 2,2' atoms or groups and by constructing a model for each molecule.

(4). There appears to be no absolute and sharp distinction between the resolvable and nonresolvable substituted diphenyls. Bell and Robinson (15) observed that the quinine salt of 4-dinitro-2,2'-dicarboxydiphenyl, which is regarded as nonresolvable, had abnormal positive rotation. Kuhn and Albrecht (83) made a similar observation on the quinine salt of 4,4'-dinitro-2,2'-dicarboxydiphenyl, and the effect was later named by Kuhn (82) as the "asymmetric transformation of the first order." Lesslie and Turner (178) found similar properties in quinine diphenate and Hyde and Adams (62) in certain substituted aryl aliphatic compounds. The phenomenon has been accepted by some chemists as evidence of labile optical isomerism. This explanation may be the proper one and may involve the effect of the presence of the two large alkaloid nuclei. The work of Hilditch (60a), however, must not be overlooked. He observed just such anomalous effects in a large variety of salts of various alkaloids with definitely inactive acids.

(5). The nonresolvability of certain phenylpyridine derivatives needs elucidation.

The development of the stereochemistry of diphenyls has stimulated the use of optical rotation for studying dynamic effects within certain molecules and has offered new methods of attack to other stereochemical problems. Bell (9a) has suggested that a cycle of the type shown below, if carried out with an optically active base, might reveal a new type of Walden inversion or perhaps give information about the mechanism of replacement of one group by another.
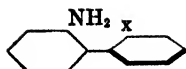
Lesslie and Turner (102) have reported the asymmetric synthesis of 2,4-dinitro-6-carboxy-2'-methyldiphenyl; the extension of their line of work may lead to interesting results. Just as Mills (127, 128, 129) and Meisenheimer (122) have applied the knowledge obtained in the study of the diphenyl field to the structure of peri-substituted naphthalenes and to the structure of oximes, still more applications to other fields may confidently be expected in the future.

The authors wish to express their sincere thanks to Dr. F. Bell of the Battersea Polytechnic, London, to Dr. W. H. Carothers of the duPont Company, and to Drs. R. L. Shriner and R. C. Fuson of the University of Illinois for their kindness in reading the manuscript and offering many pertinent suggestions.

XIII. CLASSIFICATION OF SUBSTITUTED DIPHENYLS WHICH HAVE BEEN INVESTIGATED

Before concluding this résumé it is desirable to list together the substituted diphenyls and analogous compounds which have been investigated from the stereochemical point of view. From this list the reader may get a bird's-eye view of the present status of the problem and information as to which types of compounds have not yet been studied. Certain compounds not mentioned in the previous discussion because they have no bearing on the theoretical aspects of the problem have been included.

I. *Compounds which have been resolved or of which mutarotating salts have been obtained*

(A) 2,2'-Disubstituted.
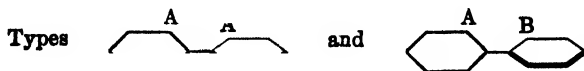
2,2'-Diiodo-4,4'-dicarboxydiphenyl (142)
2,2'-Dibromo-4,4'-dicarboxydiphenyl (143)

Diphenyl-2,2'-disulfonic acid (105)
4,4'-Diaminodiphenyl-2,2'-di-(phenylsulfonate) (104)
Monomethiodide of 2,2'-*bis*-(dimethylamino)-diphenyl (177)
2-(Diphenylhydroxymethyl)-2'-carboxydiphenyl (48)
2-(Dimethylhydroxymethyl)-2'-carboxydiphenyl (48a)
8,8'-Dicarboxy-1,1'-dinaphthyl (47, 156, 120)
8-Carboxy-8'-carboethoxy-1,1'-dinaphthyl (120)
8-Carboxy-1,1'-dinaphthyl (120)

(B) 2,2',6-Trisubstituted.

Types and
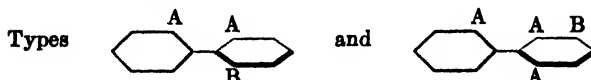
2-Nitro-6,6'-dicarboxydiphenyl (14)
2,4,4'-Trinitro-6,6'-dicarboxydiphenyl (42)
2,4'-Dinitro-6,6'-dicarboxydiphenyl (39)
2,4,6,2',4'-Pentanitro-3-carboxydiphenyl (163)

Type
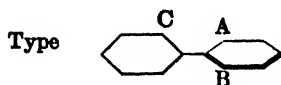
2,4-Dinitro-2'-methyl-6-carboxydiphenyl (102)
2-Methyl-6-nitro-2'-carboxydiphenyl (165)
2-Nitro-6-carboxy-2'-bromo-5'-methyldiphenyl (166)
2-Nitro-6-carboxy-2'-chloro-5'-methyldiphenyl (166)
2-Nitro-6-carboxy-2'-methoxydiphenyl (166)
2-Nitro-6-carboxy-2'-methyldiphenyl (57)
2-Nitro-6-carboxy-2'-nitrodiphenyl (57)
2-Methyl-6-carboxy-2'-nitrodiphenyl (57)
2-Nitro-6-carboxy-2',4'-dimethoxydiphenyl (194)
Substituted 2-nitro-6-carboxy-2'-methoxydiphenyl with methyl, methoxyl,
    chloro, bromo, and nitro groups at 5' position (195)
2-Nitro-6-carboxy-2',4'-dimethoxydiphenyl (58)
3,5-Dinitro-2,α-naphthylbenzoic acid (103)

(C) 2,2',6,6'-Tetrasubstituted.

Types and
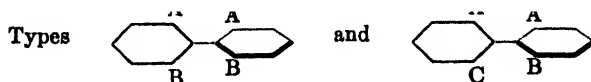
2,2'-Dinitro-6,6'-dicarboxydiphenyl (41)
2,4,2',4'-Tetranitro-6,6'-dicarboxydiphenyl (41)
2,2',4-Trinitro-6,6'-dicarboxydiphenyl (43)
2,2'-Dichloro-6,6'-dicarboxydiphenyl (40)
2,2'-Dimethoxy-6,6'-dicarboxydiphenyl (72, 161)
2,2'-Difluoro-6,6'-dicarboxydiphenyl (161)
2,2'-Dinitro-4,4'-dicarboxy-6,6'-dichlorodiphenyl (68)

2,2'-Dimethoxy-5,5'-dicarboxy-6,6'-dimethyldiphenyl (108)
2,2'-Dimethyl-6,6'-diaminodiphenyl and derivatives (121, 114, 141a)
7,8-Dimethyl-2-phenyldiphenylimidine (141a)
7,8-Dimethyl-2-keto-2,3-dihydrodiphenylimidine (141a)
2,2'-Difluoro-6,6'-diamino-3,5,3',5'-tetramethyldiphenyl (75)
2,2'-Difluoro-3,3'-dicarboxy-5,5'-dimethyl-6,6'-dinitrodiphenyl (76)
2,2'-Diamino-1,1'-dinaphthyl (87)
2,2'-Dicarboxy-1,1'-dinaphthyl (86)
2,2'-Dihydroxy-3,3'-dicarboxy-1,1'-dinaphthyl (157)
2,2'-Dinitro-1,1'-dinaphthyl-5,5'-disulfonic acid (134)
2,2'-Dicarboxy-1,1'-dianthraquinonyl (85)
2-Amino-2'-nitro-6,6'-dimethyldiphenyl (4)
2-Amino-2'-chloro-6,6'-dimethyldiphenyl (3)

Types
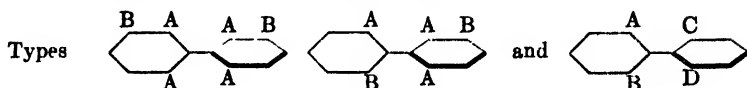
2,4,6,2',4',6'-Hexamethyl-3,3'-diaminodiphenyl (133)
2,4,6,2',4',6'-Hexanitro-3,3'-dicarboxydiphenyl (21)
2,4,6,2',4',6'-Hexachloro-3,3'-dicarboxydiphenyl (191)
2,3'-Dinitro-6-carboxy-2',6'-dimethoxydiphenyl (185)
2-Nitro-6-carboxy-2'-fluoro-6'-methoxydiphenyl (8)

(D) Phenylquinones.
    2-(3-Bromo-2,4,6-trimethylphenyl)-5-methylbenzoquinone-3,6-di(acetic acid) (60)

(E) N-phenylpyrroles.
    N-(2-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (19)
    N-(2-carboxyphenyl)-3-nitrocarbazole (135)
    1,3-Di-N-(2,5-dimethyl-3-carboxypyrryl)-2,4-dimethylbenzene (36)

(F) N,N'-Dipyrryls.
    N,N'-2,5,2',5'-Tetramethyl-3,3'-dicarboxydipyrryl (37)
    2,5-Di-N-(2,5-dimethyl-3-carboxypyrryl)-1,3-dimethylbenzene (36)

(G) Dipyridyls.
    2,4,2',4'-Tetracarboxy-6,6'-diphenyl-3,3'-dipyridyl (193)

II. *Diphenylbenzene derivatives (cis and trans forms)*

Types
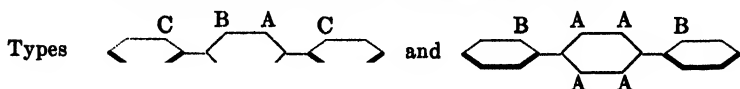
2,5-Di-(2,4-dimethylphenyl)-3,6-dibromohydroquinones and their derivatives (25)
2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinones and the corresponding quinones (148)
2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinone-di-menthoxy acetates (150)
2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetrahydroxybenzenes (149)

III. *Compounds upon which resolution has been unsuccessfully attempted*

(A) No ortho substituents.
  5,5'-Dichloro-3,3'-dicarboxydiphenyl (110)

(B) Ortho-monosubstituted.
  2-Carboxydiphenyl (11)
  2-Aminodiphenyl (11)
  1,2'-Dinaphthyl-8-carboxylic acid (120)

(C) Ortho-disubstituted.
  2,4-Dinitro-6-carboxydiphenyl (102)
  2,4-Dinitro-6-carboxy-3'-methyldiphenyl (102)
  3-Methoxy-5-methyl-2,6-dicarboxydiphenyl (70)
  Diphenic acid (63, 12)—Mutarotation of the quinine salt (178)
  4-Nitro-2,2'-dicarboxydiphenyl (10)
  4,4'-Dinitro-2,2'-dicarboxydiphenyl (44)—Dextrorotation of the quinine salt
  5,5'-Dinitro-2,2'-dicarboxydiphenyl (138)
  5,5'-Dibenzoyldiamino-2,2'-dicarboxydiphenyl (138)
  1,1'-Diamino-2,2'-dinaphthyl (115)
  2,2'-Dinitro-4,4'-dicarboxydiphenyl (15)
  4,4'-Dicarboxy-1,1'-dianthraquinonyl (160)
  2,2'-Diaminodiphenyl (114)
  2,2'-Diamino-4,4'-dimethyldiphenyl (114)
  2,2'-Diamino-5,5'-dimethyldiphenyl (114)

(D) 2,2',6-Trisubstituted.
  2-Nitro-6-carboxy-2'-fluoro-5'-methyldiphenyl (166)—Mutarotation of alkaloidal salts at 0°C.
  2-Nitro-6-carboxy-2'-methoxy-3'-methyldiphenyl (38)

(E) 2,2',6,6'-Tetrasubstituted.
  2,2',6,6'-Tetrafluoro-3,3'-dichloro-5,5'-dicarboxydiphenyl (77)
  2,2'-Difluoro-6,6'-dimethoxy-3,3'-dicarboxydiphenyl (9)
  2,2',6,6'-Tetramethoxy-3,3'-dicarboxydiphenyl (49)
  2-Nitro-6-carboxy-2',6'-dimethoxydiphenyl (185)
  2,4,6,2',4',6'-Hexanitro-3,3'-dihydroxydiphenyl (118)[17]

(F) Phenylpyrroles, phenylindoles, phenylpyridines, diquinolyls, etc.
  N-(4-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (20)
  N-(3-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (20)
  N-(2-carboxyphenyl)-2,5-dimethyl-3,4-dicarboxypyrrole (20)
  N-(2-carboxyphenyl)-carbazole (135)
  3-(2-Nitrophenyl)-2-carboxyindole (73)
  2-(2-Carboxyphenyl)-3-carboxypyridine (109)
  2-(2-Carboxy-6-chlorophenyl)-3-carboxypyridine (164)
  3-(2-Carboxyphenyl)-2,4-dicarboxy-6-phenylpyridine (164)

(G) Phenylketones, phenylethenes, etc.
  2-Carboisopropoxy-3-nitrobenzoic acid (62)

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[17] This compound should be capable of resolution. The experimental technic may be the difficulty.

2-(2-Hydroxy-4-methylbenzoyl)-3-nitrobenzoic acid (62)
p-Aminobenzoylbromomesitylene (62)
3,5-Diaminobenzoylbromomesitylene (62)
α,3,4,6-Tetramethyl-2,5-dinitrocinnamic acid (119)
4-Amino-2-isobutenylmesitylene (119)
α-Methyl-3-amino-2,4,6-tribromocinnamic acid (119)
3,3'-Diaminodimesitylmethane (113)
3,3'-Diaminodimesitylketone (113)
3,3'-Diaminodimesitylsulfone (113)

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THE STRUCTURE OF DICARBOXY COMPOUNDS FROM DISSOCIATION AND REACTION VELOCITY DATA

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A method for the determination of the structure of dicarboxy compounds from their dissociation constants has been available for several years.   Only quite recently, however, has data precise enough for a quantitative evaluation of the molecular dimensions of such compounds been secured.   An application of the principles involved to the field of reaction velocity has yielded results in excellent accordance with values obtained from dissociation constants and x-ray studies.

An elementary statistical treatment of the two dissociation constants of a dicarboxylic acid shows that a simple, definite ratio should exist between the two constants for those special cases in which dissociation of the first H^+ ion does not interfere with dissociation of the second.   In the more general case, interference effects arising from the electrical fields produced by the dissociated ions may be accounted for quantitatively by assuming a Boltzmann distribution of H^+.   The further assumption of a Coulomb field of force between the charges on the ions gives an expression for the potential energy in the vicinity of an ion involving the "length" of the dicarboxylic ion under consideration. The "length" of the molecule thus introduced into the Boltzmann relation may be calculated from suitable and sufficiently precise experimental data.

This paper reviews the development of the method and summarizes its results.   Section I presents the statistical treatment for special cases; Section II deals with the generalization of the method; Section III summarizes recent experimental results and Section IV describes the extension of the method to reaction velocity data.

I. STATISTICAL TREATMENT OF DISSOCIATION CONSTANTS

James Walker (1) in 1892 compared his conductivity measurements of the first dissociation constant (K') of dicarboxylic acids with the dissociation constant (K_α) of the monoethyl ester of the corresponding acid as shown in table 1. He made the important observation that the ratio K'/K_α, given in the last column, lies between 2 and 2.5. Three years later,. Wegscheider (2) demonstrated by statistical analysis that this ratio should be 2.

TABLE 1

Ratio of first dissociation constant of symmetrical acids to dissociation constant of corresponding monoethyl esters

ACID	FIRST DISSO-CIATION CON-STANT OF ACID K'	DISSOCIATION CONSTANT OF MONOETHYL ESTER K_α	RATIO K'/K_α
Malonic (s)	0.163	0 0451	3 6
Succinic (s)	0 0068	0 00302	2 3
Adipic (s)	0 00365	0 0025 (?)	1 3
Suberic (s)	0 00296	0 00146	2 0
Sebacic (s)	0 00276	0.00143	1.9
Methylmalonic (s)	0 086	0.0387	2 2
Ethylmalonic (s)	0 127	0.0401	3 2
Dimethylmalonic (s)	0 076	0 0304	2 5
Diethylmalonic (s)	0 74	0 0231	32 0
Fumaric (s)	0 093	0 0473	2 0
Maleic (s)	1.17	0.110	10.6
Phthalic (s)	0 121	0 0551	2 2

Consider dicarboxylic acids of the type:

$$\text{HOOC}\underset{\underset{H}{|}}{\overset{\overset{R_1}{|}}{-C-}}(CHR)_m\underset{\underset{H}{|}}{\overset{\overset{R_2}{|}}{-C-}}\text{COOH}$$
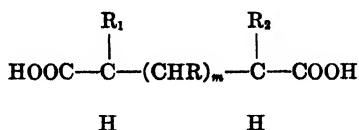
We shall call such an acid symmetrical when the radical R_1 is the same as R_2 and unsymmetrical if the radicals are different. For simplicity in representation we shall designate a symmetrical acid by the symbol HAAH, and unsymmetrical by HABH, the A and B portion of the symbol being introduced to label the particular H under consideration.

The first dissociation of an unsymmetrical dibasic acid may occur in two ways (figure 1), i.e., the H^+ at either end of the molecule may dissociate. The mass action constants for the two equilibria are:

$$K_1 = \frac{[H^+] [ABH^-]}{[HABH]}; K_2 = \frac{[HAB^-] [H^+]}{[HABH]} \tag{1}$$

Experimentally, we determine the first dissociation constant by measuring the equilibrium:

$$HABH \rightleftarrows H^+ + ABH^- + HAB^- \tag{2}$$

or:
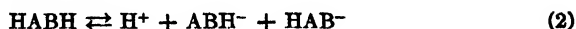
$$K' = \frac{[H^+] ([ABH^-] + [HAB^-])}{[HABH]} \tag{3}$$

By addition it follows that:

$$K' = K_1 + K_2 \tag{4}$$

An unsymmetrical dibasic acid may have two isomeric mono-ethyl esters (HAB Et and Et ABH) depending on which carboxyl
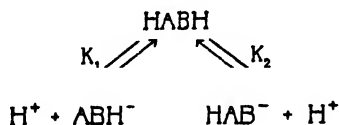
Fig. 1
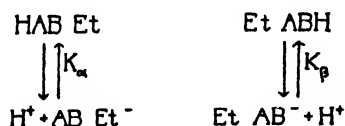
Fig. 2

group is esterified; each of these may dissociate, resulting in the two equilibria represented in figure 2. Here:

$$K_\alpha = \frac{[H^+] [AB\ Et^-]}{[HAB\ Et]}; K_\beta = \frac{[Et\ AB^-] [H^+]}{[Et\ ABH]} \tag{5}$$

Now, if we make the assumption that a hydrogen at one end of a dicarboxylic acid molecule may dissociate uninfluenced by

the groups attached to the carboxyl group at the other end, we
can say that[1]

$$K_1 = K_\alpha; K_2 = K_\beta \qquad (6)$$

Therefore:

$$K' = K_\alpha + K_\beta \qquad (6)$$

or the first dissociation constant of an unsymmetrical dicarboxylic
acid is equal to the sum of the dissociation constants of the two
isomeric monoethyl esters.

If the acid is symmetrical, $K_1 = K_2$ and, further, $K_\alpha = K_\beta$
since only one monoester is possible.   Then:

$$K' = 2 K_\alpha \quad \text{or} \quad K'/K_\alpha = 2 \qquad (7)$$

which agrees with Walker's observation.

TABLE 2

Experimental and calculated first dissociation constants

ACID	K_α	K_β	K' FOUND	K' CALCU- LATED
Succinic (s)................	0 00326	0.00326	0.0068	0.00652
Tartaric (s).......	0 046	0.046	0.097	0.092
Phthalic (s).......................	0.0656	0.0656	0.121	0.1312
Camphoric (u).......	0 000795	0.00108	0.00225	0.00188
Hemipic* (u)..........	0.016	0.130	0.145	0.146

* 3,4-dimethoxy-o-phthalic acid

The assumption of independently ionizable H^+ ions is not
limited to ethyl esters; any monoesters should give like results.
Table 2 shows the values of K_α, K_β, and K' found by Weg-
scheider for methyl esters of some symmetrical (s) and unsym-
metrical (u) acids; the last column gives the values of K' calcu-
lated by the author through equations 6 and 7.

Chandler (3), in a study of the second dissociation constants
of dibasic acids, found the ratio of the first dissociation constant
(K') to the second (K'') approximately equal to 4 at certain con-

[1] This follows since both K_1 and K_α are concerned with dissociation of H^+
at the A end of the molecule and we have assumed that the B end does not influence
dissociation at A.

centrations.   Adams (4), further developed Wegscheider's statistical treatment to demonstrate that the ratio K'/K'' should equal 4.

Let us extend figure 1 to include the second dissociation of a dicarboxylic acid:

$$HABH$$
$$K_1 \qquad K_2$$
$$H^+ + ABH^- \qquad HAB^- + H^+$$
$$K_4 \qquad K_3$$
$$H^+ + AB^=$$
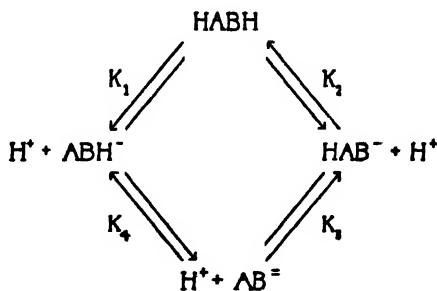
Fig. 3

The equations representing the added equilibria are given by:

$$K_3 \quad \frac{[H^+][AB^-]}{[HAB^-]}; \quad K_4 \quad \frac{[H^+][AB^-]}{[ABH^-]} \tag{8}$$

The experimentally determined second dissociation constant is represented by:

$$K'' = \frac{[H^+][AB^-]}{[ABH^-] + [HAB^-]} \tag{9}$$

From equations 8 and 9:

$$K' \quad \frac{1}{1/K_3 + 1/K_4} \quad \frac{K_3 K_4}{K_3 + K_4} \tag{10}$$

We shall now apply the general equations 4 and 10 to several types of dibasic acids.

Type I. A *symmetrical* acid with *independently* ionizable hydrogens.

Here, $K_1 = K_2 = K_3 = K_4 = K$

Equation 4 becomes $K' = 2K$ (4a)

Equation 10 becomes $K'' = K/2$ (10a)

and combining,

$$K'/K'' = 4 \tag{I}$$

which is the ratio found by Chandler.

While it is easy in practice to satisfy the condition of symmetry in a dibasic acid, sufficient separation of the two acid groups to give independently ionizable hydrogens is far more difficult. In the triphenylmethane derivatives, however, both conditions are satisfied; for phenolphthalein (5), $K'/K'' = 4.06$ and for crystal violet (6), $K'/K'' = 4.08 \pm 5\%$.

Type II. An *unsymmetrical* acid with *independently* ionizable hydrogens.

In this case, $K_1 = K_3$ and $K_2 = K_4$, since the pair K_1 and K_3 is concerned with the same H^+ at one end of the molecule while K_2 and K_4 are both concerned with the H^+ at the opposite end. (Cf. footnote 1.)

Equation 4 remains $K' = K_1 + K_2$

Equation 10 becomes $K'' = \dfrac{K_1 K_2}{K_1 + K_2}$ \hfill (10b)

Type III. *Symmetrical* and *unsymmetrical* acids; hydrogens do *not* ionize *independently*.

The majority of dibasic acids fall into this group. To obtain equations 4 and 10 for type III acids, we introduce the postulate suggested by the data that the negative charge arising in the molecule through dissociation of one H^+ diminishes the dissociation of the second hydrogen. Then:

$$K_3 < K_1 \quad \text{and} \quad K_4 < K_2$$

Equation 4 remains $K' = K_1 + K_2$

Equation 10 becomes² $K'' < \dfrac{K_1 K_2}{K_1 + K_2}$ \hfill (10c)

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² Equation 10 gives $K'' = \dfrac{1}{1/K_3 + 1/K_4}$. Since $K_3 < K_1$ and $K_4 < K_2$ then $\dfrac{1}{K_3}$ $> \dfrac{1}{K_1}$ and $\dfrac{1}{K_4} > \dfrac{1}{K_2}$. Substitution in equation 10 therefore shows $K'' < \dfrac{1}{1/K_1 + 1/K_2}$ (10c).

and combining,[3]

$$K'/K'' > 4 \qquad \text{(II)}$$

which is the general expression for symmetrical and unsymmetrical dibasic acids whose hydrogens are not independently ionizable. Table 3, taken in abbreviated form from Adams' paper, clearly shows that K'/K'' is greater than 4 in the general case.

II. GENERALIZED STATISTICAL TREATMENT OF DISSOCIATION CONSTANTS

A. Experimental relation of "n" and separation of carboxyl groups

Bjerrum (7) (1923) was the first to introduce a general quantitative treatment of dissociation constants. In accordance with

TABLE 3

Ratio of first to second dissociation constant for several dibasic acids

ACID	K'/K''	ACID	K'/K''
$(COOH)_2$	2,000	*cis* $C_2H_2(COOH)_2$	50,000
$(CH_2)(COOH)_2$	800	*trans* $C_2H_2(COOH)_2$	45
$(CH_2)_2(COOH)_2$	25	o-$C_6H_4(COOH)_2$	390
$(CH_2)_3(COOH)_2$	16.2	m-$C_6H_4(COOH)_2$	12
$(CH_2)_4(COOH)_2$	12.9	*cis* p-$C_6H_{10}(COOH)_2$	10
$(CH_2)_5(COOH)_2$	13.1	*trans* p-$C_6H_{10}(COOH)_2$	18
$(CH_2)_6(COOH)_2$	13.0	H_2SO_4	26
$(CH_2)_7(COOH)_2$	11.3	H_2SO_3	3,400
$(CH_2)_8(COOH)_2$	10.0	H_2CO_3	23,000

his terminology, we shall hereafter designate $-\log K'$ by p_1 and $-\log K''$ by p_2. As was shown in the preceding section, $K'/K'' =$

[3] From equations 4 and 10c, $\dfrac{K'}{K''} > \dfrac{(K_1 + K_2)^2}{K_1 K_2}$ For acids of type III, $K_1 \neq K_2$

or $K_1 - K_2 = a$ (or $K_2 - K_1 = a$), a being chosen positive. Then $\dfrac{(K_1 + K_2)^2}{K_1 K_2}$

$\dfrac{(2K_2 + a)^2}{K_2^2 + aK_2} = 4 + \dfrac{a^2}{K_2^2 + a}$. Since $\dfrac{a^2}{K_2^2 + a}$ is positive for type III unsymmetrical and zero for type III symmetrical acids, $K'/K'' > 4$. Acknowledgment is made to C. A. Marlies for suggesting this proof in place of the questionable method employed by Adams.

4 (I) for independent H^+ dissociation and $K'/K'' > 4$ (II) for the general case of dependent dissociation. Transposing to Bjerrum's units:

$$p_2 - p_1 = \log 4 \qquad \text{(Ia)}$$

Equation I becomes $p_2 - p_1 = \log 4$ \qquad (Ia)

Equation II becomes $p_2 - p_1 > \log 4$ \qquad (IIa)

Now define a quantity, n, by the relation:

$$n = p_2 - p_1 - \log 4 \qquad (11)$$

This n measures, in logarithmic units, the deviation of the ratio K'/K'' from the limiting value 4. When $K'/K'' = 4$, equation

TABLE 4

Dependence of n on separation, m, of carboxyl groups in the acids
$HOOC—(CH_2)_m—COOH$

ACID	m	p_1	p_2	$p_2 - p_1$	n
Oxalic	0	1.42	4.35	2.93	2.33
Malonic	1	2.80	5.69	2.89	2 29
Succinic	2	4.20	5.62	1.42	0.82
Glutaric	3	4 32	5.50	1.18	0.58
Pimelic	5	4.49	(5 36)?	(0.87)?	(0 27)?
Suberic	6	4.52	5.55	1.03	0.43
Azelaic	7	4.60	5.56	0.96	0.36
Sebacic	8	4.62	5.60	1.02	0.42

Ia holds and $n = 0$ (i.e., there is no deviation). The last column of table 4, taken from Bjerrum's paper, gives the values of n for the series of symmetrical acids: $HOOC—(CH_2)_m—COOH$.

It will be noticed that n decreases in value from 2.33 to 0.42 as the distance between the carboxyl groups increases (i.e., the deviation from the limiting ratio 4 becomes smaller, the greater the separation of the two dissociating groups). The fact that n is a function of the separation of the two carboxyl groups is further demonstrated in tables 5 and 6, where the separation of the carboxyl groups is kept constant although the nature of the acid is varied. Here n is practically a constant for a given type dibasic acid, even though the dissociation constants of the acids of that particular type vary over wide limits.

B. Quantitative relation between "n" and separation of carboxyl groups

At least two paths are open in a consideration of the influence of the first dissociation on the second:

1. Dissociation of a H^+ from a COOH may produce intramolecular forces which, upon transmission through the molecule, may affect the second dissociation. At present, no simple physi-

TABLE 5

The constancy of n for a constant separation of carboxyl groups: glutaric acid types

Glutaric acid types—(COOH groups separated by 3 C)

ACID	p_1	p_2	$p_2 - p_1$	n
Glutaric............	4 32	5 50	1.18	0.58
Thiodiglycolic*.......	3.31	4.46	1.15	0.55
Camphoric................	4 65	5.8	1 15	0 55
m-Phthalic.....	3 54	4.60	1.06	0 46

* Separation of COOH groups by 2 C and 1 S.

TABLE 6

The constancy of n for a constant separation of carboxyl groups: succinic acid types

Succinic acid types—(COOH groups separated by 2 C)

ACID	p_1	p_2	$p_2 - p_1$	n
Succinic................	4 20	5.62	1 42	0.82
d-Tartaric........	3.02	4.39	1.37	0.77
Dibromosuccinic................	1 47	2.80	1.33	0.73
Fumaric	3.03	4.47	1.44	0.84
o-Phthalic................	2.92	5.45	2.53	1.93
Maleic...................	1.93	6 29	4.36	3.76

cal picture of intramolecular forces is available for a calculation of such effects; we must rely upon experiment.

2. The negative COO^- arising from dissociation of a H^+ may attract H^+ to itself. The resultant local accumulation of H^+ around the COO^- over and above the average distribution of H^+ throughout the solution may influence the second dissociation. Such an electrostatic effect is amenable to a simple mathematical treatment.

A consideration of the most probable arrangement of a system of particles subject to the conditions that the total number of particles and their *total* energy remain constant, although the energy distribution among the particles may vary, leads to the Maxwell-Boltzmann distribution law (8) for such partition of energy among the particles:

$$C = C_0 \, \exp.^{\frac{\phi}{RT/N}} \tag{12}$$

where C = the concentration at any point,

C_0 = the average concentration throughout the system,

ϕ = the work necessary to bring a molecule from a point at concentration C to a point at concentration C_0,
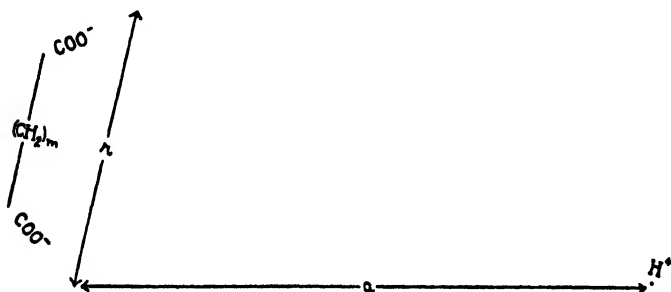
FIG. 4

R = the gas constant,

T = the absolute temperature, and

N = the Avogadro number.

The electrical work necessary to separate a positive H^+ from a negative COO^- by a distance "a" (figure 4) is given (9) by

$$\phi = \frac{e^2}{Da} \tag{13}$$

where e = the elementary charge, and

D = the dielectric constant of the medium.

Application of the Maxwell-Boltzmann law to the distribution of positive charges (H^+) in the neighborhood of a negative charge (COO^-) yields:

$$C_0 \, \exp.^{\frac{e^2 N}{DRT \cdot a}} \tag{14}$$

where C_a = the concentration of H^+ at distance "a." Physically, this tells us that the concentration of H^+ in the immediate vicinity of a negative COO^- is greater than the average H^+ concentration throughout the solution by an exponential factor involving the distance from the COO^- group. The closer we approach COO^-, the greater the concentration of H^+.

If we designate by "r" the distance between the charges on the doubly charged $^-OOC—(CH_2)_m—COO^-$ ion, or between corresponding points in the monovalent ion or uncharged molecule, equation 14 becomes:

$$C_r = C_0 \exp.^{\frac{e^2N}{DRT \cdot r}} \tag{14a}$$

The accumulation of H^+ near the second carboxyl group due to the charge on the first COO^- group might interfere with dissociation of the second H^+. With no interference, $K'/K'' = 4$ (I); in general, however, $K'/K'' > 4$ or $n > 0$. If we assume that deviation of the ratio K'/K'' from 4 arises entirely from electrostatic effects (i.e., due to the Boltzman exponential factor), then the experimentally determined logarithmic deviation n and the mathematically calculated deviation factor $\exp.^{\frac{e^2N}{DRT \cdot r}}$ may be equated:

$$\log_{10} \exp.^{\frac{e^2N}{DRT \cdot r}} \tag{III}$$

or

$$K'/K'' = 4 \exp.^{\frac{e^2N}{DRT \cdot r}} \tag{IV}$$

Thus, we have succeeded in relating an experimental value (K'/K'' or n) with "r," the "effective length" of a dicarboxylic acid molecule. Substitution of the values

$$e = 4.77 \times 10^{-10} \text{ E.S.U.}$$

$$N = 6.06 \times 10^{23}$$

$$D = 80 \text{ for } H_2O$$

$$R = 8.35 \times 10^7$$

$$T = 293$$

gives

$$\frac{3.1}{r \times 10^8} \tag{15}$$

In table 7 the values of r calculated by means of equation 15 for the acids of table 4 are shown. The separation of centers of K^+ and Cl^- in the KCl crystal is 3.14 Å. (10a) and between C—C in the diamond 1.54 Å., so that the values of r calculated above are of the correct order of magnitude.

Simms (24a) applied these calculations in an attempt to evaluate the "distortional" effects of H^+ ion dissociation. Bjerrum (7), Simms (24b), and Hückel (25) made further calculations on this basis, e.g., comparing "r" for *cis-trans* isomers and evaluating

TABLE 7

The length of some dicarboxy molecules calculated from the logarithmic deviation

ACID	m	n (table 4)	r
			Å.
Oxalic	0	2.33	1.33
Malonic	1	2.29	1.35
Succinic	2	0.82	3.8
Glutaric	3	0.58	5.3
Others	6–8	0.40	7.8

inorganic dibasic acid distances, but more precise experimental data was necessary for significant results.

III. RECENT EXPERIMENTAL RESULTS

Gane and Ingold (11) undertook an extensive and precise experimental investigation of dicarboxylic acid dissociation constants to test the applicability of Bjerrum's calculations. Previous determinations had usually been made by different methods, e.g., K' by conductivity, K'' by partition or sugar inversion experiments. A method that permitted measurement of both K' and K'' by the same experimental procedure at the same time and under the same environmental conditions was essential for obtaining suitable data. In 1924, such a method had been made available by Auerbach and Smolczyk (12).

The procedure consisted of adding small portions of sodium hydroxide to a solution of the dibasic acid and determining the pH electrometrically after each addition of alkali. Then, if

C, v = initial concentration and volume of acid,

N, x = concentration and volume of alkali after the addition of which the hydrogen ion concentration = $[H^+]$,

K', K'', K_w = the first and second dissociation constants for the acid and the water constant, respectively,

$[Na^+]$ = the concentration of sodium ion in solution, and

$[H_2A], [HA^-], [A^-]$ = the concentration of undissociated acid, monovalent, and divalent ions, respectively,

the following six equations can be set up, assuming complete dissociation of the base added and salts formed and restricting the calculation to weak acids.

$$[H^+] = K' \frac{[H_2A]}{[HA^-]} \quad \text{(16)}$$

Mass action expressions for weak acids

$$[H^+] = K' \frac{[HA^-]}{[A^-]} \quad \text{(17)}$$

$$[Na^+] + [H^+] = [HA^-] + 2[A^-] \quad \text{Electrical neutrality} \quad \text{(18)}$$

$$[H_2A] + [HA^-] + [A^-] = \frac{Cv}{v + x} \quad \text{(19)}$$

$$[Na^+] = \frac{nx}{v + x} \quad \text{(20)}$$

$$[H^+] \times [OH^-] = K_w \quad \text{(21)}$$

A solution of these simultaneous conditional equations results in the expression:

$$\frac{x}{v} = \frac{K'C \left([H^+]^2 + 2K''[H^+]\right) - \left([H^+]^2 - K_w\right)\left([H^+]^2 + K'[H^+] + K'K''\right)}{\left([H^+]^2 + K'[H^+] + K'K''\right)\left([H^+]^2 + N[H^+] - K_w\right)} \quad \text{(22)}$$

This equation contains only two unknowns, K' and K''. Therefore, any two pH measurements during titration suffice to solve

the expression for the two unknowns; the series of pH values actually determined gives a precise average value for K' and K''. To fulfill the condition of complete dissociation of alkali and salts, dilute solutions (approximately 0.06 to 0.0007 M) were used by Gane and Ingold; further, calculations for oxalic acid by this

TABLE 8

More precise values of the length for the series HOOC—$(CH_2)_m$—COOH

ACID	m	$K' \times 10^5$	$k'' \times 10^6$	r
				$\mathring{A}$.
Oxalic	0	......	. ..	....
Malonic	1	177.0	4.37	1.5
Succinic	2	7.36	4.50	5.0
Glutaric	3	4.60	5.34	9.2
Adipic	4	3.90	5.29	11.5
Pimelic	5	3.33	4 87	13.2
Suberic	6	3.07	4.71	14 5
Azelaic	7	2.82	4.64	16.8

TABLE 9

Effect of substitution of radicals on length of dicarboxylic acid molecule

ACID	$K' \times 10^5$	$K'' \times 10^6$	r
			$\mathring{A}$.
Glutaric	4.60	534	9.22
Substituted glutaric acids			
β-Methyl	5.77	62.8	2.27
β-n-Propyl	4.97	43.2	2.12
β,β-Dimethyl	20.3	55.1	1.57
β,β-Diethyl	30.4	7.85	1.02
β,β-Di-n-propyl	20.3	5.42	1.01
Cyclo acids			
Cyclopentane-1,1-diacetic	16.8	26.3	1.40
Cyclohexane-1,1-diacetic	33.6	10.2	1.04
Cycloheptane-1,1-diacetic	27.8	10.9	1.10

method were excluded because K' does not follow the mass action law. Table 8 summarizes the K' and K'' values determined by this method for the series HOOC—$(CH_2)_m$—COOH, and the "r" values calculated from Bjerrum's equation (IV).

An empirical expression satisfactory for the last five acids,

$r = 4.4 + 1.73\,m$, assigns a value of 1.73 Å. increase per additional CH_2 group and points to a straight or zigzag chain rather than a coiled structure for these aliphatic acids. The deviations exhibited by the first two may be attributed to internal polar effects which increase with shortening of the chain.

The structure of several substituted dicarboxylic acids was next determined by this method (13). A short summary of results is given by table 9.

In the case of unsubstituted glutaric acid, $r = 9.22$ Å., whereas substitution of one methyl or propyl on the central carbon reduces the distance between the carboxyl groups to about 2 Å.; substitution of two radicals cuts the distance to 1 Å. Apparently, substitution on the central carbon tends to coil the long chain acid, thereby bringing the carboxyl groups closer (figures 5a, 5b).

COOH
CH_2
H_2C
CH_2
COOH

CR_2
H_3C CH_2
HOOC   COOH
b

CH_2
H_3C CH_2
H_3C c CH_2
H_3C CH_2
HOOC   COOH
c
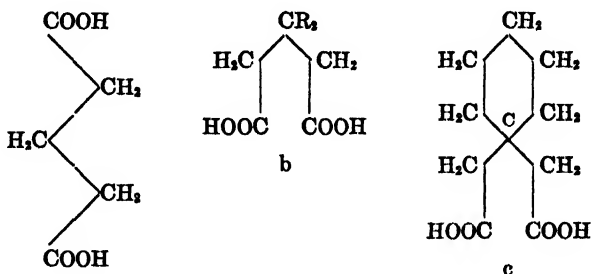
Fig. 5

The r values for cyclic (figure 5c) 1,1-diacetic acids (table 9) are in harmony with the coiled structure (figure 5b) assigned to substituted glutaric acids. This structure is in further accord with much chemical evidence and is believed by Ingold to support the valency deflection hypothesis (14).

Among the most serious disturbances to calculations of this type are effects caused by polar transmission through the molecule and by local variations in the properties of the medium. Internal transmission effects may be disregarded when the carboxyl groups are separated by more than two carbon atoms (cf. table 8).

Solvent disturbances were studied by Gane and Ingold in a fourth paper (15). Correction for interionic effects were made by

titrating each dibasic acid at several concentrations in the very dilute region and extrapolating to $\mu = 0$.[4] Table 10 shows an example of this type of correction.

Corrections for solvent effects caused by compressibility of the solvent in the neighborhood of an ion, by anisotropy (electrical and optical) and by association are treated in Ingold's "Remarks on the Electrical and Mechanical Conditions in the Neighborhood of a Dissolved Ion" (16). A method of approximations yields an

TABLE 10

Corrections for interionic effects

ACID	10^3C	$10^4K'$	$10^7K''$
Malonic...................	5.000	17.7	41.2
	4.991	17.7	43.7
	2.000	15.8	25.5
	1.000	15.3	24.3
	1.000	15.4	23.8
	0.400	15.1	21.1
	0.125	14.9	21.2
	$\mu = 0$	14.9	20.3
Succinic...................	5.000	0.734	46.1
	4.880	0.736	45.0
	2.000	0.678	37.8
	1.000	0.659	36.6
	0.400	0.648	35.0
	0.125	0.644	33.5
	$\mu = 0$	0.641	33.3

expression for the potential, ψ, in the vicinity of an ion corrected for the above factors, taking the form of a series in terms of

$$\left[\frac{a'e}{r} + \frac{a''e^2}{r^3} + \right.$$

instead of the simplified form used by Bjerrum (equation 13).

Another question examined is that of the flexibility of the molecule (15). An equation for K'/K'' was derived for flexible mole-

[4] μ = ionic strength = $\Sigma \frac{1}{2}$ molar concentration × (valence of ion)^2.

cules on the assumption that a definite maximum, r_{max}, and a definite minimum, r_{min}, separation exists between the carboxyl groups. The distribution of undissociated molecules and monovalent ions is such that there are as many of these with length, r_1, as with length, r_2, within the limits set by r_{max} and r_{min}. In the case of the divalent ions, however, there are more (Boltzmann distribution) with larger r's than with smaller lengths since the repulsion of the like charges at each end of the divalent ion tends to stretch it. Since the energy necessary to stretch the molecules to the lengths calculated on this basis is very great, it is concluded

TABLE 11

Length of dicarboxy molecules calculated from corrected dissociation data and from assumed zigzag chain model

ACID	m	r_{obs}	r_{calc}	Δr
		$\stackrel{.}{A}.$	$\stackrel{.}{A}.$	$\stackrel{.}{A}.$
Oxalic...........................	0	(3.37)	(3.54)	(−0.17)
Malonic.............................	1	3.43	4 26	−0.83
Succinic.....................	2	5.58	5.87	−0.29
Glutaric.............................	3	7.11	6.84	+0.27
Adipic..............................	4	8 22	8.36	−0.14
Pimelic.............................	5	9.43	9.43	0.00
Suberic.............................	6	11.07	10.88	+0.19
Azelaic.....................	7	12.03	12.04	−0.01

that the dicarboxy molecule has a rigid structure. Thus, Gane and Ingold propose that a major portion of the force tending to maintain a favored configuration in crystals, liquids, and dilute solutions is intramolecular and not externally electrostatic in origin.

The column (r_{obs} Å.) of table 11 was calculated after applying all the above noted corrections. Its values may be expressed by the linear equation, $r = 2.98 + 1.29\ m$ Å., indicating an increase of 1.29 Å. per CH_2 group, a value well in accord with x-ray data (10c, 17).

When $m = 0$, $r = 2.98$, a measure of the distance between the charges in two COO^- groups. The distance between the charge on the COO^- and the carbon of this group measured along the

line connecting the two carbons in the molecule (figure 6) is
calculated to be 1.00 Å. Using this result together with a zigzag
model for the dicarboxylic acids and the appropriate trigo-
nometrical relations, column 4 of table 11 was obtained. The
last column shows deviations between values calculated from ob-
servational data and from the zigzag model. The good agree-
ment points to a rigidly extended zigzag configuration for dicar-
boxylic acids in dilute aqueous solutions.
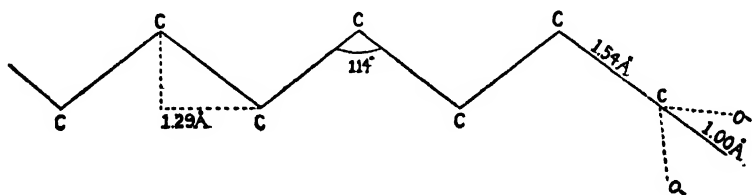
FIG. 6
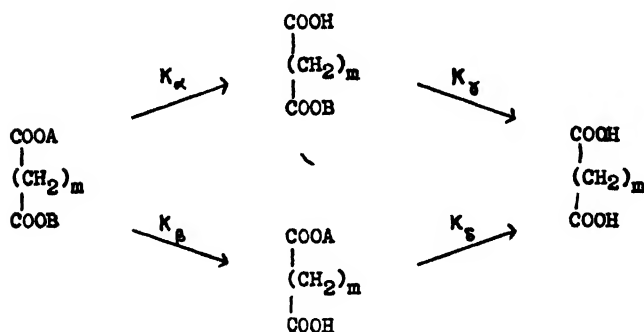
FIG. 7

IV. APPLICATION TO REACTION VELOCITY DATA

A general formula relating to the several velocity constants
of hydrolysis of a polyester was statistically derived by Ingold (18)
assuming no interaction of the ester groups. The present author
submits the following simplified derivation to illustrate the
method for the hydrolysis of a diester.

Let k_α, k_β, k_γ, k_δ, and v_α, v_β, v_γ, v_δ, be the specific velocity con-

stants and the velocities of acid hydrolysis of the corresponding
stepwise reactions represented in figure 7.   Then,

$$v_\alpha = \frac{v_-}{[AB]}, \; k_\beta = \frac{v_\beta}{[AB]}; \; k_\gamma \frac{v_\gamma}{[BH]}; \; k_\delta = \frac{v_\delta}{[AH]} \tag{22}$$

If k_1 and k_2 are the experimentally determined first and second
hydrolysis constants of the diester, and v_1 and v_2 the experimen-
tally measured velocities, then:

$$v_1 = k_1[AB] = v_\alpha + v_\beta = (k_\alpha + k_\beta)\,[AB] \tag{23}$$

or

$$k_1 = k_\alpha + k_\beta \tag{24}$$

and

$$v_2 = k_2\,([AH] + [BH]) = v_\gamma + v_\delta \tag{25}$$

But

$$[AH] + [BH] = \frac{v_\gamma}{k_\gamma} + \frac{v_\delta}{k_\delta} \tag{26}$$

therefore

$$k_2 \left[\frac{v_\gamma}{k_\gamma} + \frac{v_\delta}{k_\delta} \right] = v_\gamma + v_\delta \tag{27}$$

For a symmetrical ester (A = B) with independent hydrolysis
at each end of the chain,

$$k_\alpha = k_\beta = k_\gamma = k_\delta = k$$

and

Equation 24 becomes $k_1 = 2\,k$ (24a)

Equation 27 becomes $k_2 = k$ (27a)

or, combining,

$$k_1/k_2 = 2 \tag{28}$$

Thus, the ratio of the first to the second velocity constants of
hydrolysis should be 2 for a symmetrical ester without inter-

action of the two ester groups. Table 12 abbreviated from Ingold (18) shows experimental values for the acid hydrolysis of some symmetrical esters; the k_1/k_2 ratio found is closely equal to 2.

TABLE 12

Experimental and calculated ratio of first to second velocity of acid hydrolysis constants for some diesters

ESTER	$k_1 \times 10^3$	$k_2 \times 10^5$	k_1/k_2 FOUND	k_1/k_2 CALCULATED
Dimethyl succinate	2 40	121	1.98	2.00
Diethyl succinate	2.30	121	1 90	2.00
Dimethyl d-tartrate....	1 24	62	2 00	2.00
Diethyl d-tartrate..........	1.40	68	2 06	2.00

TABLE 13

Length of dicarboxy molecules calculated from velocity constant and from dissociation constant ratios

ESTER	k_1/k_2	MEAN k_1/k_2	MEAN r FROM VELOCITY DATA	r FROM DISSOCIATION DATA
Dimethyl oxalate........	(10⁴)	(10⁴)	(2.9)	(3.37)
Diethyl oxalate........................	(10⁴)			
Dimethyl malonate.....................	(92)	(91)	(3.8)	3.43
Diethyl malonate......................	(90)			
Dimethyl succinate....................	9.66	9.64	5.62	5.58
Diethyl succinate.....................	9.62			
Dimethyl glutarate....................	6 45	6.42	6.83	7.11
Diethyl glutarate.....................	6.40			
Dimethyl adipate.....	4.95	4.97	8.30	8.22
Diethyl adipate..................	5.00			
Dimethyl pimelate.....................	4.34	4.34	9.57	9.43
Dimethyl suberate....................	3.91	3.91	10.97	11.07
Dimethyl azelate......................	3.61	3.61	12.38	12.03

This limiting ratio of 2 is found not to hold for the alkaline hydrolysis of diesters, nor would we, in the light of the Brönsted theory of reaction velocity (19, 20a), expect the preceding simple assumptions to hold. We are dealing with charged ions in the second stage of alkaline hydrolysis.

The first step of the reaction between the diester and the OH⁻ ion may be represented by the formation of the intermediate complex:

$$ROOC—(CH_2)_m—COOR + OH^- \rightarrow ROOC—(CH_2)_m—COOR \cdot OH^-$$
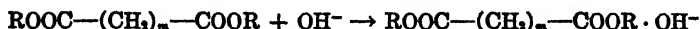
with reaction taking place between an uncharged molecule and a negative ion.

In the second stage, however, the following reaction between two like charged ions will occur:

$$ROOC—(CH_2)_m—COO^- + OH^- \rightarrow HO^- \cdot ROOC—(CH_2)_m—COO^-$$
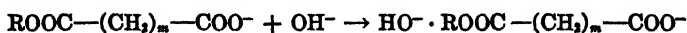
The presence of a charged COO⁻ group will cause a decrease of like charged OH⁻ ions in the immediate vicinity of COO⁻. Consequently, there will be a decrease in the number of critical complexes below the number that would form in the absence of charge effects.

We would not expect k_1/k_2 to equal 2 for alkaline hydrolysis, but

$$k_1/k_2 = 2 \exp.^{\frac{\phi}{kT}} \tag{29}$$

where the Boltzmann exponential factor once again takes care of electrostatic influences. The potential term, ϕ, here too involves the distance, "r," between the charges on the COO⁻ groups (assuming the OH⁻ to form a critical complex at the carboxyl group).

By employing the modified expression for ϕ (16) and working in dilute solutions to correct for interionic effects, Ingold (21) obtained the following values of k_1/k_2 (table 13) for the alkaline hydrolysis of some diesters. The "r" values were determined by means of equation 29. The last column, giving r values calculated from the dissociation constant ratio (table 11), shows excellent agreement and indicates a zigzag model for both dicarboxy esters and dicarboxylic acids.

It must be emphasized that this method is by no means restricted to dicarboxy compounds but provides a perfectly general way of calculating molecular dimensions from the proper data. La Mer (20b) has made a similar calculation for the thiosulfate-

bromoacetate ion and ester reaction and secured a very reasonable "length" for the bromoacetate molecule.

At the date of writing this review, an attempt by Eucken (22) to use this method for calculating various molecular properties (e.g., internal dielectric constant of a molecule) of a series of substituted organic acids has appeared. MacInnes (23) has obtained an interesting relationship for a group of substituted monocarboxylic acids which is in harmony with calculations of the Bjerrum type.

These recent applications serve to emphasize the generality and utility of this method of attack on molecular properties in solution; many interesting results may be awaited from similar calculations.

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THE MECHANISM OF HETEROGENEOUS CATALYTIC ORGANIC REACTIONS. I

CATALYTIC HYDROGENATION[1]

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The process of catalytic hydrogenation of organic compounds is of great interest, not only industrially but also scientifically. It comprises the hydrogenation of fatty substances, the hydrogenation of carboxides with formation of methanol, and a host of other important chemical processes. In order to master these reactions the most important step is to understand their mechanism.

In hydrogenating fatty oils one or more double bonds between carbon atoms are converted into single bonds; in hydrogenating carboxides one or more double bonds between carbon and oxygen atoms are reduced. This seems to be a close analogy; nevertheless the mechanism of the two processes is probably quite different, as we shall see later.

We consider first the mechanism of the hydrogenation of multiple carbon bonds. For a long time I have adhered to the theory (1) that catalytic hydrogenation of multiple carbon bonds belongs to the great class of catalytic reactions that are produced by ions. I am glad now to have the opportunity of surveying the facts which seem to me to prove that ionic catalysis is involved in this type of hydrogenation.

But first, what is ionic catalysis?

Ostwald (2) and Arrhenius (3) were the first to find that ions

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[1] This is the first of a series of three articles. II, The Dissociation of Carbon Bonds, is scheduled for publication in Volume XIII of This Journal, and III, The Formation of Carbon Bonds, in Volume XIV.—Editor.

[2] Written in English by the author.

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are catalysts. Ostwald showed that the velocity of saponification of esters and that of inversion of cane sugar are much accelerated by adding inorganic or organic acids. Then Arrhenius
found that there is a direct relation between the electrical conductivity of the acids and the acceleration of the reaction. Electrical conductivity is, as Ostwald found, a measure of dissociation. In aqueous solutions of acids we have as dissociation
products the various anions, the radicals of the acids, and the
hydrogen cation. This last is the only ion present in all these
catalytic reactions, and therefore we conclude that the hydrogen
ion is the catalyst. This conclusion is confirmed by the fact that
the concentration of the hydrogen ions is, to a first approximation, proportional to the acceleration of the velocity of reaction,
as Ostwald, Palmaer, and Goldschmidt have found (4).

But what is the mechanism of these reactions, in which the
positively charged hydrogen atom, the proton, is the catalyst?

The proton is the smallest ion we know; its radius is perhaps
smaller than 10^{-13} cm., while the radius of Na^+ is 10^{-8} cm. (1
Å.). The field power, F, equals Q/r^2; therefore F of the spherical
proton is at least 10^{10} times larger than that of the sodium ion.
Therefore the proton strongly deforms all known ions, dipoles,
and molecules.

On bringing it into water, the proton combines with water
molecules to form a complex, namely, the especially stable H_3O^+,
surrounded by spherical layers of water dipoles, which are directed toward the central ion. All the reactants in the hydrolysis
of cane sugar or in the hydrolysis or formation of esters, i.e.,
water, cane sugar, alcohols, esters, and undissociated acids, are
dipoles and can substitute each other in the complex formed by
the H_3O^+ ion; all these dipoles are reinforced by the electric field
of the central ion,—reinforced, polarized, deformed, and *activated.*

And now we have in a single complex each participant in the
reaction beside the other. The activated water and the activated
cane sugar molecule are thus joined for a relatively long time.
They combine and react to give glucose and fructose.

Born and Franck (5) have shown in a very important paper
that the catalyst is characterized by two properties,—the *deform-*

ing of the reactants and thus the activating of them, and the *bringing them closely together for a time.* These are the two significant features of our picture of the hydrolysis of cane sugar.

The most important property of the catalyst is its power of deformation. It is not sufficient that the participants in the reaction merely lie together for a time. Charcoal absorbs hydrogen and ethylene in fairly large amounts, but they do not combine. We suppose that the activation of hydrogen by deformation is in this case not sufficient.

By the polarization of the reactants their centers of electric gravity are separated. We get dipoles, the electric field of which is much stronger than that of an undeformed organic compound. In many cases this deformation leads to dissociation, as, for instance, Meerwein (6) has shown in the reaction between zinc chloride and water:

$$ZnCl_2 + H_2O = (ZnCl_2OH)' + H^{.}$$
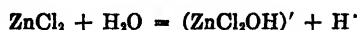
By forming the complex $(ZnCl_2OH)'$ the dipole water is ionized and gives the $H^{.}$ ion, which is much more active than the hydrogen of the water molecule itself.

The substances which take part in a catalytic reaction are generally very inert. Thus we find that inversion of cane sugar does not take place in an aqueous solution which is free of catalyst. This means that the energy of activation is so large that it cannot be delivered under these conditions. Cane sugar is a dipole and has therefore a certain activity; homopolar gases, such as hydrogen, oxygen, and nitrogen, are much more inactive. In agreement with the quantum-mechanical investigations, made by London, Heitler, and Polanyi (7), we must suppose that the molecules are surrounded by a potential wall which knocks off other molecules coming along. We need the activation energy for surmounting the potential wall. Since the catalyst lowers the energy necessary for activation, we presume that its action consists of a deformation of the participants in the reaction.

Work is needed to lower the potential wall. If we bring a typically heteropolar substance, such as an acid, into water then the acid is dissolved in water and is dissociated into its ions.

Born's cyclic diagram represents the factors as follows:

$$\text{HCOOH} \xrightarrow{\ +\ aq\ +\ L\ } \underset{\uparrow\,aq}{\text{H}^+} \quad + \quad \text{HCOO}^-_{aq} \tag{1}$$

$$-I \qquad +aq+H_{\text{H}^+} \qquad +aq+H_{\text{HCOO}^-}$$
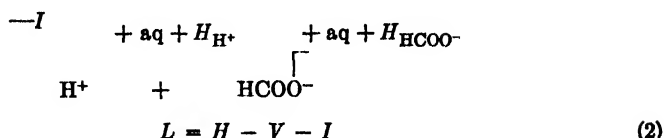
$$\text{H}^+ \quad + \quad \text{HCOO}^-$$

$$L = H - V - I \tag{2}$$

$$H = H_{\text{H}^+} + H_{\text{HCOO}^-} \tag{2a}$$

where L is the heat of solution, H the heat of hydration of the ions, V the heat of evaporation, and I the heat of ionization. L and V generally have values of several Calories and I of some hundred, so that H, the sum of the energies of hydration, must have a large value and delivers the energy needed for the ionization of the acid.

Born has shown that the energy of solution can be calculated approximately by a very simple method (8). He finds

$$H = 1/2 \left(1 - \frac{1}{k}\right) \frac{z^2 e^2}{r_i} N \cdot F \text{ Cal.} \tag{3}$$

where k is the dielectric constant of the solvent, z is the charge on the ion, r_i is its radius, F is the equivalent value of the erg in Calories (2.388×10^{-11}), and N is Avogadro's number (6.06×10^{23}). Therefore the heat of solution is greater at high values of k and z and at small values of r_i. Because the heat of solution furnishes the energy needed for ionization the three important factors are: *greatness of k and of z and smallness of r_i*.

The two types of catalysis, i.e., homogeneous catalysis in water, produced by hydrogen ions, and heterogeneous catalysis in metals with hydrogen, both occur in media of high dielectric constant. The value of k for water is 81; the value for metals is not determinable, but is very high. In formula 3 we can therefore neglect the value of $1/k$ which is very small, and we get very large values for H if r_i is less than 1×10^{-8} cm. and z has a higher value than 1.

In homogeneous catalytic reactions, in which the hydrogen ion is the real catalyst, we have seen that the ion activates the reactants by deforming (polarizing, ionizing) them and that it brings together the activated participants for a long enough time to allow them to react. The mechanism of heterogeneous hydrogen catalysis is not identical with this but the principal features are obviously the same. We ask, what ion is here the catalyst? But before we answer this question we must discuss another explanation.

It is generally supposed that hydrogen is sorbed by metals in the form of atoms and that therefore the hydrogen atoms are the active factors in this type of catalysis (10). This is based on the fact that the sorption of hydrogen by metals often follows the square root relation,

$$c = k \sqrt{p} \qquad (4)$$

where c is the quantity of sorbed hydrogen, p the pressure in the gas phase, and k a constant. According to the distribution law, the molecular hydrogen is so distributed between the solid and gaseous phases that for a given temperature and pressure the concentration in the two phases has a fixed proportion

$$[H_2]_{gas}/[H_2]_{solid} = k_1 \qquad (5)$$

On the other hand the molecular hydrogen, dissolved in the solid phase, is in equilibrium with its products of dissociation:

$$[H]^2_{solid}/[H_2]_{solid} = k_2 \qquad (6)$$

Therefore we have

$$[H]^2_{solid} = k_3[H_2]_{gas} \qquad (7)$$

For a given temperature the concentration of a gas in the gas phase is proportional to its pressure, so that we have

$$[H]_{solid} = k_4 \sqrt{p} \qquad (8)$$

If we assume that the dissociation of hydrogen is practically

complete in the solid phase, then [H] is a measure of the total quantity of sorbed hydrogen and we have

$$H_{\text{dissolved}} = k \sqrt{p} = kp^{1/2}$$

which is equation 4, as found empirically.

This is the usual explanation of the validity of the square root relation. If there is dissociation, we must have this relation; but the reverse conclusion does not necessarily follow. Equation 4 is only a special form of the general equation of the isotherm of adsorption, given by Freundlich:

$$p = kp^{1/n} \tag{9}$$

where $1/n$ is a proper fraction and n can have values from 10 to 1 (11).

We ignore the physical significance of n in this empirical formula and it seems therefore impossible to draw conclusions from the fact that in the above cases n is often equal to 2, as Sieverts and his coworkers found (12).

Not in all cases of sorption of hydrogen by metals is n exactly equal to 2. Thus Sieverts (13) found that for palladium the following equation is valid:

$$c = k \sqrt{p} + k'p \tag{10}$$

In this case one might suppose that a part of the hydrogen is dissociated and the rest is not. By contracting equation 10 we find a value for $1/n$ which lies between 1 and 1/2. But $1/n$ can also have values smaller than 1/2. Chappuis has found, for instance, that $1/n$ has a value of 0.184 in the sorption of ammonia by meerschaum (14). It is of course impossible to give a rational explanation on the above basis for a value of $1/n$ which is smaller than 1/5.

There are still other substances which sorb hydrogen according to the square root relation, e.g., charcoal, as found by McBain (15). But charcoal is not a catalyst for hydrogenation; it is quite indifferent at moderate temperatures.

On the other hand we know that double bonds are easily at-

tacked by atomic hydrogen, as v. Wartenberg and Schulze (16) and also Bonhoeffer and Harteck (17) have found. In the gaseous state the reaction is complex. Ethylene gives not only the product of hydrogenation, ethane, but also acetylene; by the enormous development of heat, caused by the reaction of atomic hydrogen, a portion of ethylene is dehydrogenized and gives acetylene. It is probable that in the solid phase the reaction is not so complex because the heat of reaction is here conducted away much more easily.

Since charcoal, nevertheless, has no catalytic action in the hydrogenation of ethylene, it seems improbable that the hydrogen sorbed by charcoal is to an appreciable extent in the atomic state. We therefore cannot agree with the conclusions drawn by Winkelmann and by Coehn from the square root relation (10, 74).

On the other hand I do not imply that there is no possibility that atomic hydrogen is present on or in catalytic metals. On the contrary we shall see that it is often present. That explanation of catalysis seems, however, to be wrong.

One of the reactants, the unsaturated hydrocarbon, has a moderate dipole moment when unsymmetrical; but the other, hydrogen, has none. The heat of activation is very large for hydrogen, small for the unsaturated hydrocarbons. It is often sufficient to activate only hydrogen; e.g., atomic hydrogen hydrogenates the double bonds of carbon, as Bonhoeffer has shown (18). Therefore it seems sufficient to investigate the manner of activating hydrogen in this type of catalysis.

First we ask which elements, or compounds of elements, are able to hydrogenate multiple carbon bonds.

THE CATALYTIC ELEMENTS ARE EFFECTIVE ESSENTIALLY AS SUCH

There is no doubt that the hydrogenating properties of catalysts are connected with the metallic state. Bedford and Erdmann (19) for a time advanced the opinion that the suboxides of metals, and especially Ni_2O, are catalysts; but this opinion was an error and their Ni_2O was only a mixture of NiO and Ni. Oxides of metals are effective only at a temperature at which they are reduced by

hydrogen. Nevertheless we must emphasize that it is not at all necessary that the whole catalyst or the greater part of it be present as metal. In many cases the catalyst is effective even when large amounts of unreduced oxides or sulfides are present.

The simple technical catalysts for hydrogenating multiple carbon bonds are made by employing compounds of elements, the oxides of which are easily reducible. Hydrogen is the reducing agent and the compounds are oxides or such other compounds as easily go over into oxides by heating, viz., carbonates, nitrates, oxalates, etc. Thus the metals are obtained in a finely divided state, very favorable for hydrogenation. The reduction of the easily reducible oxides involves mostly *development of heat* and follows the equation:

$$MeO + H_2 = Me + H_2O + Q$$

The reduction of the difficultly reducible oxides requires *absorption of heat.*

In order to determine the conditions for obtaining these metals from the oxides we employ the Nernst theorem. We use it in the approximate formula and always write the equations so that the reaction takes place with the development of heat as read from left to right. Thus for a reaction which absorbs heat we write

$$Me + H_2O = MeO + H_2 + Q_1$$

In the first case

$$K_p = p_{H_2}/p_{H_2O}$$

in the second

$$K_p = p_{H_2O}/p_{H_2}$$

If we set $p_{H_2} = 1$, we have $K_p = 1/p_{H_2O}$, or p_{H_2O}, respectively. The approximate formula of Nernst's theorem

$$\log K_p = -\frac{Q}{4.571\ T} + \Sigma \nu\ 1.75 \log T + \Sigma \nu C$$

is in this case simplified, because the second member on the right side is zero; $\Sigma \nu C$ is equal to -2 or to $+2$ respectively. Table 1

gives the heat of formation, B, of the oxides of metals, the heat of reaction, Q, and the value p_{H_2O}/p_{H_2} for $p_{H_2} = 1$ for a number of oxides of metals.

Table 1 shows that the partial pressure of water vapor is very small in the state of equilibrium for the difficultly reducible oxides.   For hydrogen, saturated with water vapor, we find the proportion p_{H_2O}/p_{H_2} at 18°C. and 1 atmosphere to be $2 \times 10^{-2}A$. Therefore it is impossible to reduce ferrous oxide at 400° A. with moist hydrogen.

For thermodynamic reasons it is impossible that in the state of equilibrium an oxide be only partly reduced to metal at a given

TABLE 1

Heat of formation, B, heat of reaction, Q, and p_{H_2O}/p_{H_2} in the state of equilibrium

OXIDE OF METAL	B	Q	p_{H_2O} FOR $p_{H_2} = 1$	
			$T = 400°A.$	$T = 800°A.$
	Calories	*Calories*		
Ag₂O	+6.5	+51 4	1×10^{30}	1×10^{16}
CuO	+37.8	+20.1	1×10^{13}	$3\ 2 \times 10^{7}$
PbO	+52.7	+5.2	6.9×10^{4}	2.6×10^{3}
NiO	+54.7	+3 2	5.6×10^{3}	7.5×10^{2}
CoO	+57.5	+0.4	1.7×10^{2}	1.3×10^{2}
FeO	+65.0	−7.1	1.3×10^{-2}	1.2
ZnO	+83 0	−25 1	1.9×10^{-12}	1.4×10^{-6}
MnO	+90 8	−32.9	1×10^{-16}	1×10^{-7}
CaO	+145 0	−87.1	2.5×10^{-46}	1.6×10^{-22}

temperature; above the equilibrium pressure we have only oxide, below it only metal, provided there are two solid phases and not a solution.   But in many cases the normal progress of the reduction is hindered by sintering, which may be considerable, as I have shown in the case of finely divided nickel (20).   Thereby inertness is produced and a part of the oxide is not reduced.   In some cases the reduction of nickel oxide, NiO, or ferrous oxide, FeO, leads to final states which are still rather far from the quantitative reduction to metal, as Taylor and Starkweather have shown (21).

Sieverts (27) has found that the solubility of gases is often greater in an oxide of a metal than in the metal itself.   Hence the

presence of an oxide promotes sorption and therefore the catalytic activity, as Willstätter has shown (22).

But in what manner can we produce finely divided elements, the oxides of which are hard to reduce? This must be known in order to solve the question as to what elements have hydrogenating properties, since hydrogenation is caused not only by the presence of a suitable metal, but also by its finely divided state, i.e., its great exterior or interior surface.

The figures of table 1 are valid for the state of equilibrium. But the reaction

$$MeO + H_2 = Me + H_2O$$

can also be employed when the equilibrium is unfavorable. We must then quantitatively remove the water formed by reduction. But the speed of this reaction is generally very small. It is only at high temperatures (1000–2000°C.) and pressures that the difficultly reducible oxides such as Cr_2O_3, V_2O_3, Nb_2O_5, can be reduced, as v. Wartenberg, Broy, and Reinicke have shown (23).

But such methods cannot be used because they give crystallized metals of small surface which are unable to catalyze the hydrogenation. However, the reduction of an oxide which is accompanied by absorption of heat can be effected at lower temperature, provided we bring this oxide together with another one that is easier to reduce and provided that the metal of the second oxide gives an alloy or a mixed crystal with the metal of the first. In this case the absorption of heat is lowered by the heat of formation of the alloy or of the mixed crystal, and therefore the partial pressure of steam in the equilibrium rises.

Thus zinc oxide is much more easily reduced by hydrogen in the presence of cupric oxide than when alone. The reason is that the heat of formation of an alloy of zinc and copper is positive and especially large if the content of copper is large, as Baker has shown (24). v. Wartenberg and his coworkers have found (23) that even oxides which are very hard to reduce, such as the oxides of yttrium, zirconium, and thorium, are reducible in the presence of metals with which they can alloy. In practice we often use mixtures of easily and difficultly reducible oxides of

metals. The latter are known as promotors or activators, e.g., the oxides of chromium, molybdenum, tungsten, and vanadium.

It has not been known whether these elements in a state of large surface have catalytic properties for hydrogenation, because we did not know methods for producing them. However, in some cases we can get these finely divided metals by heating the amalgams at moderate temperatures in a high vacuum for a long time (25). Thus we can get chromium in a finely divided state. It is a hydrogenating catalyst of high activity. The amalgam of manganese also gave a strongly active metal.

The elements of the first and second group, i.e., the metals of the alkalies and alkaline earths, can be prepared in an active state if the metals are sublimed in high vacuum, then diluted in dry, liquid ammonia and precipitated on quartz beads by evaporating the ammonia (25). Pease and Stewart have applied a similar, though not so effective, method (26).

WHAT ELEMENTS HAVE HYDROGENATING PROPERTIES IN A STATE OF LARGE SURFACE AREA?

We shall investigate the hydrogenating properties of metals in a state of large surface area by using them as catalysts in the hydrogenation of ethylene. We test only the simple elements without any additions, because it is otherwise impossible to determine which component of a mixture is really effective and which is the activator. We use only mild conditions of reaction: $t = 0$ to 200°C., $P = 1$ atmosphere.

A large number of papers has been published on the hydrogenation of ethylene at moderate temperature and pressure. The results are given in table 2.

Ethylene is very easily reduced by hydrogen; an active nickel catalyst hydrogenates ethylene at −100°C. with great velocity (25). So this reaction is useful in revealing even a slight activity. Column 2 of table 2 gives a rough evaluation of the activity of the element in question; this evaluation is only a rough approximation, and serious objections might be raised against it because it is often impossible to get two different elements into comparable states for hydrogenation.

Yet though it is often impossible to establish fine distinctions, we find in many cases differences large enough to justify the above rough evaluation. Of course, it is necessary to make sure in every case that no contact poisons or sintering effects have inadvertently lowered the activity and that no undoubtedly active elements have increased it. In most cases the evaluation of the activity

TABLE 2

The activity of finely divided metals in the hydrogenation of ethylene

0 = inactive; 1 = slightly, 2 = moderately, 3 = strongly active

METAL	ACTIVITY	REFERENCE	METAL	ACTIVITY	REFERENCE
Group 1			Group 4		
Na	0	(28)	Pb...	0	(36)
K...	0	(28)	Group 5		
Rb...	1	(25)			
Cs....	2	(29)	As....	0	(37)
Cu..	3	(30)	Bi	0	(38)
Ag...	0	(31)	Group 6		
Au.	0	(32)			
			Cr	3	(25)
Group 2			Group 7		
Ca.........	2	(33)			
Sr	2	(25)	Mn	3	(25)
Ba	2	(25)	Re.....	2	(39, 25)
Zn....	0	(34)	Group 8		
Hg	0	(35)			
			Fe.................	2	(40)
Group 3			Co...............	3	(41)
			Ni.................	3	(42)
Ce.........	0 (?)	(25)	Pd.....	3	(43)
Tl..	0	(25)	Pt.................	3	(44)

was based not only on the measurements of other authors, but also on my own.

The situation concerning zinc is not clear. Zinc has a high affinity for oxygen; when finely divided it goes rapidly over into zinc oxide in the presence of oxygen. Zinc oxide is not reducible with hydrogen under mild conditions, as we have seen. Maxsted

(34) has found that zinc is a contact poison for platinum and palladium.

On the other hand, Mittasch (34) has found that a contact mass made by reducing a mixture of zinc oxide, chromic oxide, and uranium trioxide is an excellent catalyst for hydrogenating ethylene.   In a previous paper (34) I have reported that finely divided zinc, made by a reaction between zinc chloride and magnesium in alcoholic solution, hydrogenates ethylene.   In a more recent investigation (25) I was unable to repeat this result when using a well-cleaned zinc chloride.   Other methods also did not give an active zinc, so that I now believe that pure, finely divided zinc is not able to hydrogenate ethylene under mild conditions.

If we locate the active elements in the curve of atomic volumes, given in figure 1, we find them in two opposite places.   (1) At the maxima of the curves of the long periods, the alkali elements with large atomic volumes and the alkaline earths.   In this series the activity increases with increase of atomic volume.   However, the activity of these elements is low or moderate.   (2) At the minima of the curves of the long periods, the elements of the eighth group and copper, chromium, and rhenium.   The activity of these elements is high and generally increases with decrease of atomic volume.   The atomic volume decreases in the series iron, cobalt, nickel, while the activity increases (1).

The atomic volume, V, is determined by the relation $V = A/D$, where A is the atomic weight and D the density.   The dimensions of the space required by a single atom are given by the expression $f = \sqrt[3]{V/N}$ where N is Avogadro's number.   In many cases f corresponds approximately to the distance between the atoms of the crystallized element (47).

If we assume that the atoms are spherical, we have, according to Meg Nad Saha (60), the simple relation:

$$I_1/I_2 = r_2/r_1 \tag{11}$$

where I_1 and I_2 are the ionization potentials of the elements E_1 and E_2 and r_1 and r_2 are their radii.

This relation is exact only if the elements compared have a similar electron structure.   But for our rough calculation it is

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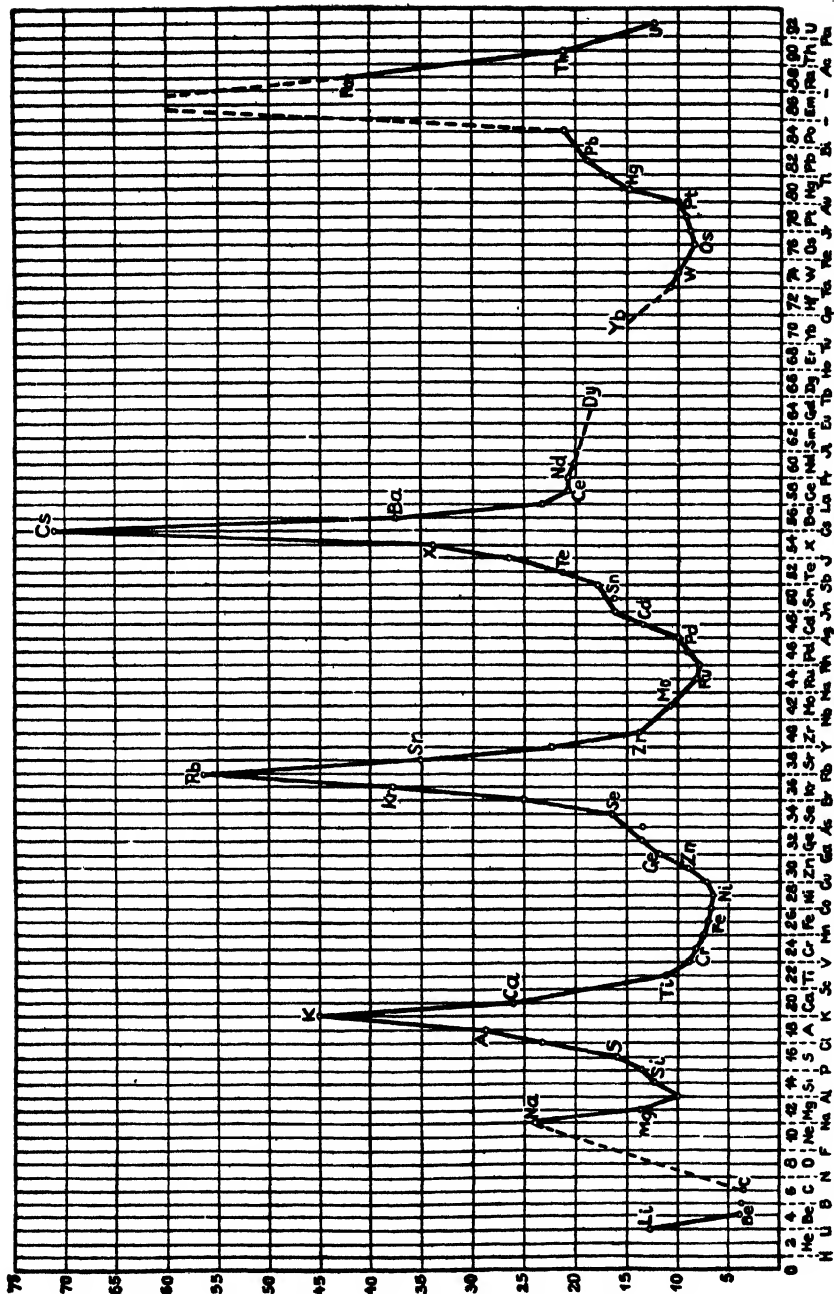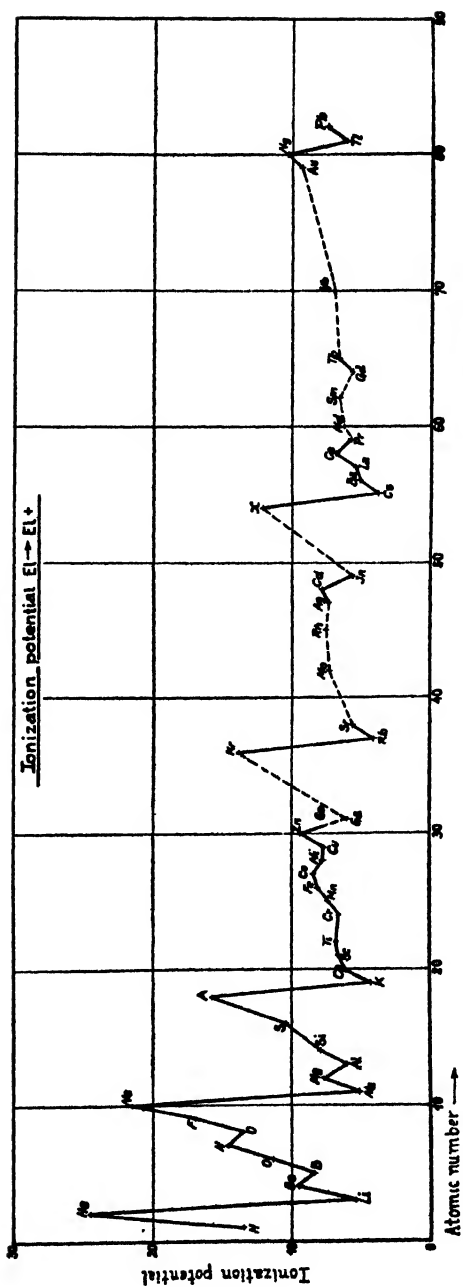
Fig. 2. Relation of Ionization Potential to Atomic Number

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permissible to assume that large atomic volume means a large atomic radius and therefore, according to equation 11, also a low ionization potential. The relation between r and f is not exactly 1:2, but we may assume it as a first approximation. Then the ionization potentials of the elements of the first class would be much smaller than those of the second. This, indeed, is the case, as shown in figure 2.

Generally the work function ϕ, i.e. the work needed to remove an electron from a metallic surface, is smaller than the ionization potential I. There is a similar difference between the work functions of the elements of the first and second class; the work function is small in the first class and large in the second.

The values for I and ϕ in equivalent volts ($\phi = eV$) for the two groups of metals are:

	Na	K	Rb	Cs	Ca	Ba	Fe	Co	Ni	Cu	Pt
I. .	5 1	4.3	4 2	3.9	6.1	5 2	8 1	7 8	7.6	7 7	8.9
ϕ...	1.8	1.6	1 5	1 4	2.2	1 9	4 0	4 3	4.4	4.0	5 5

The work function, ϕ, of the elements of the first class is lowered in mixtures of metals and oxides, as is the case in the oxide cathode tubes (47) which contain mixtures of elements and oxides of the first class. The work function for the Siemens tube O. C. No. 4 is 0.83 volt and for B. O. No. 585 is 0.64 volt, as Rothe found (48). These energies are of the order of heats of adsorption, and thus can easily be attained.

While the work function in these elements is small so that electrons are easily emitted from their surfaces, the situation on the surface of a metal of the second class is quite different, for the work function is large. If we bring a volatile metal of the first class, such as rubidium, on to the heated surface of a metal of the second class, then the rubidium atom loses its electron and leaves the surface as a positive ion. Therefore heating an element of the first class produces electron emission at low temperature; heating a metal of the second class produces at low temperature (400–500°C.) emission of positive ions of the alkalies, which are always present in commercial metal.

In the interior of a metal we have free electrons, according to

the electron theory of metals; the number of these electrons corresponds to the number of valency electrons, as Houston (50) has found.

Because the alkali metals are univalent, the charge on their ions is only 1; their radius is large and therefore the force of the electric field, F, is weak.

Table 3 gives the values of the ionic radii, using the figures of Goldschmidt, (G), (51) and Pauling, (P), (52).   Because $F = Q/r^2$, the field in the immediate vicinity of Ba^{++} would be 3.6 times weaker than in that of Ni^{++}, if we can consider the ion as a charged sphere, the charge of which is concentrated at the center. But we can do so only when the number of exterior electrons is

TABLE 3

Values of the ionic radii

	Li^+	Na^+	K^+	Rb^+	Cs^+	
(G)................	0 78	0 98	1.33	1.49	1.65	
(P)..	0.60	0 95	1.33	1.48	1.69	
	Mg^{++}	Ca^{++}	Sr^{++}	Ba^{++}		
(G)................		0 78	1.06	1.27	1 43	
(P)......		0.65	0.99	1.13	1.35	
	Fe^{++}	Co^{++}	Ni^{++}	Cu^{++}	Zn^{++}	
(G)................		0.83	0.82	0 78	0.83 (extra-polated)	0.83

large, as in the case of Ni^{++}, where there are 16.   For Ba^{++} there are only 8 and therefore the field of Ba^{++} in its immediate vicinity is still weaker, because the potential of repulsion is equal to b/r^n and n is a function of the number of exterior electrons (58). Barium belongs to the first, nickel to the second class; the stronger electric fields are always in the second class.

There is still another important difference between the two classes.   All elements belonging to Class 2 are "gap elements" in the sense of Thomson and Bohr, as shown in figure 3.   In this figure the "gap elements" are enclosed in brackets.   They are those in which the last interior electron shell is not yet filled, though there are already electrons in the exterior shell.

A characteristic property of the salts of these "gap elements" is the formation of colored solutions in water. As Fajans has shown (45), the color of the aqueous solution is produced by the deformation of water molecules by the ions of these metals. Copper, which is not enclosed by brackets in figure 3, also belongs
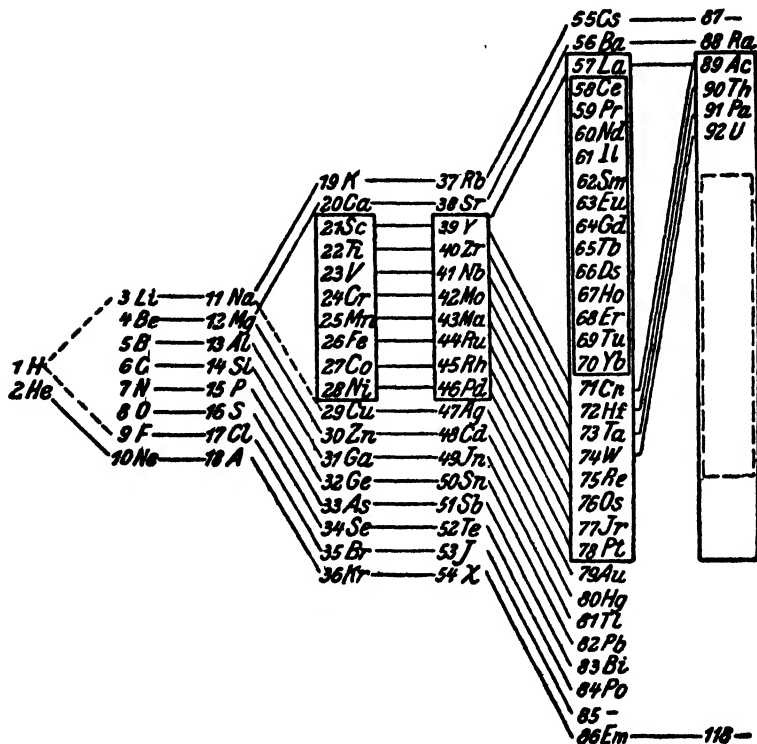
FIG. 3. PERIODIC SYSTEM OF THE ELEMENTS BASED ON ATOMIC STRUCTURE
(J. J. Thomson, N. Bohr)

to this class of elements. It gives colored solutions in the divalent state, though solutions of univalent copper are colorless. In the spectrum of atomic copper part of the lines correspond to an alkali type with a complete M shell and only one valence electron. The arrangement of electrons is:

$$2 \ \big| \ 2 \quad 6 \ \big| \ 2 \quad 6 \quad 10 \ \big| \ 1$$

The other lines belong to an atomic type which is produced by the passing of a $3d$ electron out of the M shell to $4s$, with this arrangement of electrons resulting:

$$2 \quad 6 \quad \Big| \quad 2 \quad 6 \quad 9$$
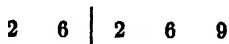
This type corresponds to the "gap elements."

Colored solutions are characteristic of multiply charged ions. In Class 2 we have only multivalent elements; the ions carry a charge of at least 2. They also have small ionic radii, shown in table 3. A small radius, together with multiple charges on the ion, produces a strong electric field and a strong polarization of the atoms and molecules. This gives the conditions necessary for the deformation and activation of participants in a reaction.

TABLE 4

Values of the heat of formation, Q, of the hydrides of the alkalies and alkaline earths

HYDRIDE	Q/H_2	AUTHOR
LiH	43 2	Moers (51)
NaH	25 6	Hagen and Sieverts (52)
CaH$_2$	46 6	
SrH$_2$	42.2	} Guntz and Benoit (53)
BaH$_2$	41.0	

Elements of Class 1, on the other hand, have weak electric fields. They presumably operate in hydrogenation by a mechanism quite different from that of Class 2.

We have still to discuss one last important difference between the two classes. In the first class hydrides are formed easily and are solids with the properties of real salts, as Moers has found (51). The heat of formation of several hydrides is known (see table 4).

In the second class, on the other hand, only copper hydride is known as a well-defined compound; but under *extreme conditions* a series of hydrides of the metals have been spectroscopically found and measured by Mecke (54). The heat of formation of cuprous hydride is negative; Sieverts found it to be − 10.2 Cal. and showed that it is a derivative of univalent copper (55).

The existence of other hydrides of this class formed at room temperature seems to be doubtful. According to Schlenck and Weichselfelder, nickel hydrides, NiH_2 and NiH, may be formed by the reaction between nickel chloride, phenylmagnesium bromide, and hydrogen in ether (56). I was unable to verify the formation of these compounds. In any case, if they exist, all hydrides of the second class are very unstable. The probability of their formation from the elements under ordinary reaction conditions is very small.

For calculating the dissociation pressure of these hydrides by the Nernst theorem the equation of dissociation is written:

$$2CuH = 2Cu + H_2 + 10,240 \text{ cal.}$$
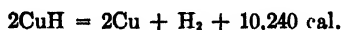
$$\log K_p = - \frac{Q}{4\,571\ T} + 1.75\ \Sigma\nu \log T + \Sigma\nu C$$

where

$$\Sigma \nu = - 1$$

and

$$\Sigma\nu C = - 1.6;\ K_p \quad {}^1 \quad p_{H_2}$$

The resulting dissociation pressure at the absolute temperature, T, is:—

$T =$	300	373	473
$p_H =$	10^{13}	10^{12}	10^{11}

Therefore at equilibrium the cuprous hydride must be completely dissociated into hydrogen and copper at the above temperatures and at the pressure of 1 atmosphere. At high temperatures the formation of cuprous hydride, CuH, is possible, but at low temperatures it is very improbable.

The nature of the hydrides of the second class can be determined by measuring the exponents of the potentials between the metal and the hydrogen atoms In the molecule, MeH, forces of attraction and repulsion are effective; their dependence on the

distance, r, between the two nuclei is a very different function of r in the two cases.   The potential, P, is the sum of the potential P_p of the attractive forces and the potential P_q of the repulsive forces.   Assuming that the forces are purely radial, we have

$$P = P_p + P_q = - e^2 \frac{C_p}{r^p} + e^2 \frac{C_q}{r^q}$$

where e is the charge of the electron, C_p and C_q constants, p the exponent of attraction, and q that of repulsion.   If we have attraction according to Coulomb's law, then p is equal to 1.   This is the case if we have a heteropolar binding of ions with complete shells of electrons. q is a number greater than 1.

The evaluation of spectroscopic data of the hydrides, MgH, CuH, AuH, gives the figures $p = 1$, $q = 3$ to 4.   Thus quasipolar binding must be assumed (Mecke).   The halogen hydrides give the same values.   The halogen hydrides in the gaseous state are not purely heteropolar compounds.   We must suppose that the proton has largely deformed the halogen ion and has entered into it.   The molecule of the halogen hydride in the gaseous state is thus an intermediate stage between a heteropolar and a homopolar compound; we call it quasipolar and express by this term that it is nearly polar.

In most cases hydrogen is sorbed by the metals of the second class with formation of a solid solution, as Hoitsema has proved for the system PdH_x (57).

Now we can characterize the two classes of catalysts.   (1) To the first class belong uni- and multi-valent elements, including the alkalies and the alkaline earths, which form stable, solid, salt-like hydrides, and which lie at the maxima of the atomic volume curve.   Their atomic radius is large, their ionization potential low, their work function small.   Among the alkali metals the catalytic activity increases with increase of atomic radius and varies from 0 to 2.   (2) To the second class belong the divalent elements of the iron and platinum groups and other members of these groups which (like iron) have a minimum valence of 2, or (like copper) a maximum of 2.   They do not give stable, solid hydrides but form solid solutions of hydrogen, such

that the content of hydrogen for a given piece of metal depends on the pressure and the temperature, and such that there is a reversible equilibrium of adsorption or solution under definite conditions of volume and surface of the metal, temperature, and pressure. These elements lie at the minima of the long periods of the atomic volume curve. Their atomic radius is small, their ionization potential high, their work function large. All elements lying at the minima of the long periods—and therefore the elements of Class 2—are "gap elements" in which the last interior shell of electrons is incomplete. In the iron group the activity increases with decreasing atomic radius, and is always large, with a value of about 3.

THE RELATION OF THE TWO CLASSES OF ACTIVE ELEMENTS TO THE PERIODIC SYSTEM

The two classes of active elements are on opposite sides of the atomic volume curve, the first at the maxima, the second at the minima of the long periods. There remain two minima in the short periods, including the elements beryllium, boron, carbon, magnesium, aluminum, and silicon. These have no catalytic properties under ordinary conditions. They are not "gap elements" and therefore are not included in the definition of the second class. It seems probable that the activity of the "gap elements" is due to the presence of unshared electrons in the incompleted inner shell.

Furthermore, the elements at the minima of the short periods have a valency of more than 2 and do not form solid hydrides. Their hydrides are gaseous, as are those of tin, lead, phosphorus, arsenic, and antimony. All these elements have no catalytic properties, whether their atomic volume be large or small. The reason for their inactivity is thus not only the lack of unshared electrons but also the inertness of their hydrides. Nearly all solid elements which give gaseous hydrides have a valence of 3 or 4.

Since there is a continuous transition from the heteropolar to the homopolar state in the halogen hydrides, for instance, we may consider the metal hydrides as a first approximation to be hetero-

polar.   We may assume that the ions are rigid spheres.   Then in a molecule, MeX_n, the central ion will be more protected the more enveloping ions there are, and the larger is the ratio of the radius of the enveloping ion to the radius of the central ion.   For methane we find r_{H^-} = 2.08 (Goldschmidt) and $r_{C^{4+}}$ = 0.2, whence the value of the ratio is 10.   Therefore we must assume that the field of the central ion is largely protected by the four negative ions, and that this central ion can no longer exert a noticeable attraction on the negative ions or electrons of a neighboring molecule.   The attraction is weak and can be broken by heat vibration.   Such compounds therefore will have a low boiling point and show the inert behavior of methane.

To this class of hydrides belong the volatile stannic hydride, SnH_4, and lead hydride, PbH_4.   Once they are formed they cover and then poison the catalyst by their inertia.   The enveloping of the central ion is of course most complete with the hydrides of the type MeH_4.   Here the ions are arranged around the central ion in the form of a tetrahedron; owing to the symmetrical structure the dipole moment is equal to zero.

With compounds of the type MeH_3 the H^- ions are distributed at the corners of a triangle.   In this case a complete envelopment is scarcely possible, and we therefore find higher boiling points than with the MeH_4 hydrides.   The dipole moment is no longer equal to zero (see table 5).

A high energy of dissociation accompanies the symmetrical configuration of the inactive hydrides of the type MeH_4.   The work needed to remove an atom of hydrogen from the molecule of methane is about 90(115) Cal., as Mecke (p. 393) has shown, which is about as great as the work needed to dissociate the hydrogen molecule.   Therefore carbon has no catalytic properties at moderate temperatures.

We have seen that there are three groups of elements which react with hydrogen in a different manner:—the first group gives solid hydrides, the second gives solid solutions or adsorption, the third gives gaseous hydrides.   If we add as a fourth group those elements which do not react with hydrogen, then we can arrange all elements according to their behavior with hydrogen.   If we

TABLE 5

Boiling points and dipole moments of volatile hydrides

HYDRIDE	BOILING POINT	DIPOLE MOMENT
	degrees C.	
CH₄ .	−161	0
SiH₄ ...	−112	0
GeH₄...	−90	0
SnH₄ .	−52	0
NH₃.	−33	1.5
PH₃.	−86	0.55
AsH₃	−55	0.15
SbH₃	−17	0.1

HYDRIDE	BOILING POINT	DIPOLE MOMENT
	degrees C.	
CH_4 .	−161	0
SiH_4 ...	−112	0
GeH_4...	−90	0
SnH_4 .	−52	0
NH_3.	−33	1.5
PH_3.	−86	0.55
AsH_3	−55	0.15
SbH_3	−17	0.1

TABLE 6

Periodic system of the elements in Staigmuller's arrangement

TABLE 7

Energy of formation of hydrides

| METAL	GRAM ATOMS Me ON ONE MOLECULE OF HYDROGEN	ENERGY OF FORMATION PER MOLE OF HYDROGEN
		calories
Li...	2	43,200
Na	2	25,600
Ca	1	46,600
Sr	1	42,200
Ba	1	40,960
Ce	0.75	42,260
Pr	0.74	39,520
La	0.75	40,090

use the periodic system in the form given by Staigmüller (59), then these groups fall into definite positions, as Paneth has already shown (60), and as is evident from table 6.

The two classes of active elements correspond to Staigmüller's Groups 1 and 2. The first class and the first group are almost identical except for the elements of low atomic weight. They contain the elements which give salt-like hydrides of the type of lithium hydride, LiH; but, as Sieverts has found (61), there are also salt-like hydrides in the family of rare earths. The energy of formation per mole of hydrogen is almost the same for the hydrides of the alkaline earths as for those of the rare earths, as shown in table 7. On the basis of the energy of formation of the hydrides and their stability, the elements cerium, praseodymium, and lanthanum, which are in Staigmüller's second group, belong to his first. The atomic volume curve shows that the atomic volumes of these elements are much smaller than those of the alkalies and alkaline earths. The work function is larger and amounts to 3.0–3.3 volts in the series cerium to lanthanum. In accord with the point of view here developed, I was unable to effect hydrogenation of ethylene with cerium as catalyst at a temperature of 200°C.[3] The activity of the rare earth elements, if existent, is therefore small.

The fundamental difference between the two classes of active elements is given by the value of their atomic volume and their structure (i.e., as gap elements). The atomic volume is roughly proportional to the atomic radius and is inversely proportional to the ionization potential and to the work function.

### MECHANISM OF REACTION IN CLASS 1.—AFFINITY OF THE HYDROGEN ATOM FOR THE ELECTRON

The work, D_{H_2}, needed to dissociate H_2 into 2H, amounts to 100 Calories and is so large that it cannot be supplied under ordinary conditions in the gas phase.

$$H_2 \rightarrow 2H - Q; \quad Q = 100 \text{ Cal.}$$
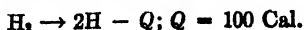
[3] British patent 325,695, however, states that cerium is a hydrogenation catalyst at 300°C.

If there are free electrons, Q is reduced by the affinity of the hydrogen atom for electrons, E_H, provided that it is positive:

$$H_2 + 2\bar{e} \rightarrow 2H^- - Q'; Q - 2E_H$$
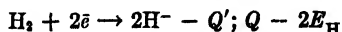
Until recently the value of E_H was in doubt. Joos and Hüttig (64) made the first calculation and gave a value of $+$ 23 Cal. But Kasarnowsky and Proskurnin (65) were able to show that this calculation was in error, because it made use of an incorrect value for the density of sodium hydride. They found $E_H = -$ 1 Cal. But this figure also was of dubious value because it was based on very doubtful figures for the heat of sublimation of the alkali metals. At last Hylleraas (66) has calculated this value by the use of wave mechanics and has found $E_H = +16.3$ Cal. This value was confirmed by Bethe (67) and is very well founded theoretically. We shall use it in the following. If we set $E_H = 16.3$ Cal., we have

$$H_2 + 2\bar{e} = 2H^- - 67.4 \text{ Cal.} \tag{13}$$

in the gas phase.

Reaction 13 will start more easily if H_2 is deformed by an electric field. In this case the polarized molecule H_2^* is involved and the energy needed according to equation 13 is lowered.

It is very probable that the electron takes part in the activation of hydrogen in Class 1, for we have seen that only those elements of this class are active whose work function is small enough to be available under mild conditions. The heat of formation of the alkali hydrides is about 10 Cal., excepting for lithium hydride, for which it is 21.6 Cal. (68). The dissociation according to the equation:

$$MeH = Me + 1/2 H_2 - Q''$$

must take place easily because Q'' is small. But this reaction does not give atomic hydrogen; the work required for producing 2H in the gas phase in this way is still $2Q''$ in excess of 100 Cal.

But in the solid phase the situation is different. The hydrides of the alkalies crystallize in the type of sodium chloride, though it is possible that cesium hydride crystallizes in the similar type of

cesium chloride. The hydrogen has the function of a negative ion. The affinity, E, of the hydrogen atom for the electron is, however, distinctly less than that of halogen atoms:—

	H	F	Cl	Br	I
$E =$	0.71	4.0	3 8	3.0	3 1 volts

Therefore the attraction of the second electron of H^- is small. H^-, according to Goldschmidt, has a radius, r_i, as large as that of the iodide ion.

	H^-	F^-	Cl^-	Br^-	I^-
$r_i =$	2.08	1.36	1.81	1.95	2.16

The structure of H^- is therefore very loose.

Fajans has shown that in the series

CuF_2	$CuCl_2$	$CuBr_2$	CuI_2
colorless	yellow-brown	brown-black	unstable

the color becomes gradually more dark; he explains this by the increasing deformation of the electron envelopes, caused by the strong field of the doubly charged small ion of copper. The increase of coloring is the consequence of the tendency of the ions to become deformed, which increases from F^- to I^- and can be measured by refractometric data. At the end of the series is cupric iodide, which is unstable. Here the deformation of I^- has become so great that the electron is split off and neutral atoms, and hence molecules, are formed:[4]

$$2Cu^{++} + 4I^- \rightarrow 2CuI + 2I \rightarrow 2CuI + I_2 \qquad (14)$$

Because the affinity of H for the electron is much less than that of I, and the volumes of the two ions are nearly the same, we should expect a hydride to be still less stable than an iodide, provided the electric field of the cation is the same. From this point of view it is very interesting that cuprous hydride, CuH, is a derivative of monovalent copper, as Sieverts has shown (55), and that cupric hydride, CuH_2, does not exist. In the latter the electric field of the copper ion is much stronger.

[4] The radius of Cu^+ is much greater than that of Cu^{++} (i.e., 1.27 and 0.83 Å respectively).

It therefore seems very improbable that a hydride of nickel, NiH_2, can exist, as Schlenck and Weichselfelder suppose (56). In the strong field of Ni^{++}, H^- cannot exist and must be converted immediately into H or H_2. Indeed I could find no indication of the existence of a nickel hydride in repeating the above experiments.

The dissociation

$$MeH_2 \rightarrow MeH + H \rightarrow Me + 2H$$

which we must assume in analogy with equation 14, will occur in every case to a greater or less extent,—the more easily when the energy needed is small. The energy is especially small in a medium of high dielectric constant.

Hüttig and Krajewski conclude from measurements of the dissociation pressure of lithium hydride that a part of the hydrogen ions are free and mobile in the lattice structure. They use the expression "vagabond hydrogen" (69). We have in the interior of the hydride crystal an equilibrium

$$H^- \rightleftharpoons H + \bar{e}$$
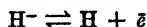
since the work needed to dissociate is small even in the gas phase and is still smaller in a medium the dielectric constant of which is much greater than 1. H travels much more easily than H^-, because its radius is 0.5 Å, only a fourth of that of H^- (2.08 Å, according to Goldschmidt).

In the series of alkali metals only rubidium and cesium proved to be active. In the alkaline earth series all the elements are active, i.e., calcium, strontium, and barium.

It is very probable that hydrides are intermediate products in the action of metals of the first class as catalysts for hydrogenating ethylene. The dissociation pressures of these hydrides are considerably under 100 mm. at temperatures under 350°C., as Ephraim and Michel have established (77). Therefore they are stable at a pressure of 1 atmosphere and a temperature of 150–250°C.

Hill and Kistiakowsky have found that cesium hydrogenates ethylene at room temperature, but that this reaction is hindered

after a short time by formation of cesium hydride, CsH (29). Cesium hydride is very stable at room temperature and reacts only slowly with ethylene, though more quickly at higher temperature.   I have found that cesium reacts rather quickly with a mixture of ethylene and hydrogen at 200°C. and gives ethane. At this temperature this hydrogenation can be carried on with sufficient velocity for a long time.   The stability of cesium hydride at room temperature seems to me not incompatible with the supposition that it delivers the active hydrogen to the hydrogenation at 200°C.

Therefore we may expect that formation of hydrides takes place at the surface, but that the formation of active hydrogen occurs at any distance beneath the visible surface in the interior of the crystal, where the active points of the catalyst are located. We presume that the active form of hydrogen for hydrogenation with the first class of catalysts is the *hydrogen atom*.

We therefore formulate the hydrogenation of ethylene in this class as follows:—

$$C_2H_4 + 2H = C_2H_6$$

THE MECHANISM OF THE REACTION FOR ELEMENTS IN CLASS 2

In the first class of active elements we have formulated the process of activation with regard to the ease of formation of free electrons at the surface:

$$H_2 + 2\bar{e} = 2H^-$$

$$2H^- + 2Me^+ = 2MeH$$
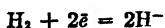
and have seen that the hydrides dissociate in the interior of the lattice to give H^- and H.

In the second class a similar reaction is impossible since the work function is large and the concentration of electrons at the surface must be extremely small or equal to zero.   The probability of the formation of hydrides is also very small.

In the interior of a metal the valence electrons are free and mobile; hence the atoms themselves must be present as ions. The ions of the second class carry strong electric fields in their vicinity.

We may expect the following reactions:

$$H_2 \qquad H_2^*$$

$$H_-^* \rightarrow H_-^+ + \bar{e}$$
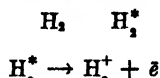
Here H_2^* means a deformed hydrogen molecule. H_2^+ is unstable. With an energy of 2.5 volts, it dissociates according to the equation

$$H_2^+ \rightarrow H^+ + H$$

The whole process

$$H_2 \rightarrow H^+ + H + \bar{e} \qquad (15)$$
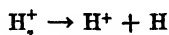
requires 17.88 volts, as Birge has shown (69).

It is very remarkable that this amount of energy is nearly identical with the second potential of ionization in this class, as is shown in table 8 (70).

TABLE 8

Ionization potentials of the elements of the second class

	FIRST POTENTIAL	SECOND POTENTIAL
Cr..............................	6.74	16.6
Fe.....	8.06	16.5
Co...	7.81	
Ni..........	7 64	18.2
Cu.......	7.69	17.8 (20.5)
Pd..	8.1	19.8 (?)

For copper two second potentials of ionization are known (71). They correspond to the transitions:

$$Cu^+ \quad 2 \qquad 10$$

$$2 \qquad 9 \qquad \text{20.5 volts}$$

$$Cu^{++} \quad 2 \qquad 9 \qquad \qquad \text{17.8 volts}$$

The process

$$Me^{++} + H_2 = Me^+ + H^+ + H^0 \qquad (16)$$
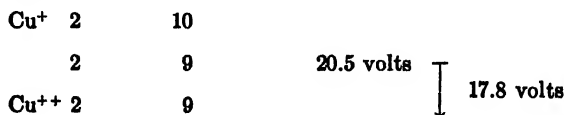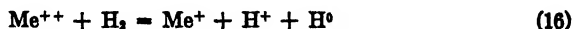
in the above cases therefore requires no energy or only a small amount.   Kallmann and Rosen have shown that in the gaseous phase a reaction of exchange between charged and uncharged cor-

puscles takes place when the ionization potentials of both are nearly equal (78). We are inclined to suppose that the equality of the ionization potentials of H_2 according to equation 15 and of $Me^+ \rightarrow Me^{++}$ in this class is not merely accidental.

THE PRESENCE OF POSITIVE IONS IN THE INTERIOR OF THE METALS OF THE SECOND CLASS

There is no doubt that there are positive ions of hydrogen in the solution of hydrogen in some metals, especially in metals of Class 2. Thus Janitzky concluded, from his measurements of the resistance of wires charged with gas, that the gases dissolved in the metal are dissociated into positive ions and electrons and participate in the conduction of current (72). Similar observations were made by Smith who employed hydrogen (73). But Coehn and Specht and Coehn and Jürgens were the first to furnish incontestable experimental proof that hydrogen dissolved in palladium travels with the positive current and must be present, at least in part, in the form of positive ions (74, 75). Coehn and his coworkers used wires of palladium or of an alloy of palladium and silver, which were electrolytically charged with hydrogen. The possibility thus remains that the protons taken up electrolytically were the cause of the traveling effect. I was able to show (25) that molecular hydrogen, dissolved by the wire at room temperature under pressure, shows the same phenomena as electrolytic hydrogen.

Positively charged hydrogen molecules, H_2^+, have a volume of the magnitude of molecular hydrogen and cannot travel in many lattices because the interstices are too small. They are dissociated at the expense of a small amount of energy,

$$H_2^+ \rightarrow H^+ + H_0$$
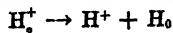
with the formation of protons and atomic hydrogen.

The stability of the solution of hydrogen in the metal at ordinary temperature is very remarkable. The dissolved hydrogen does not leave the metal, even though it sometimes travels in various directions with the current, and even though the wire may be in a medium free of hydrogen.

Similar observations could not be made with other metals. The phenomena with platinum, copper, iron, and nickel are different; if hydrogen comes into contact with these metals, either in molecular form under pressure or electrolytically in the form of ions, no noticeable change of resistance is found (25). It is evident from figure 4 that the amount of hydrogen dissolved in
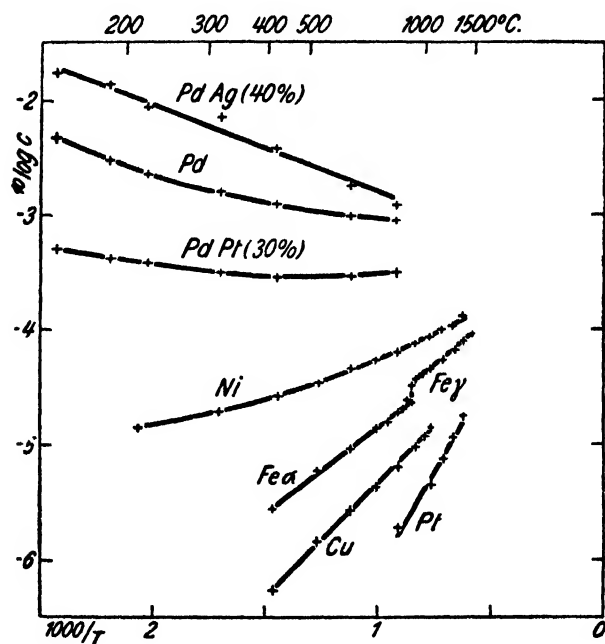
FIG. 4. RELATION OF SOLUTION PRESSURE OF HYDROGEN TO TEMPERATURE FOR VARIOUS METALS

these metals at moderate temperatures is very small in comparison with palladium–silver and palladium. (The figure is taken from Borelius who used the data of Sieverts (76).) Therefore the question whether positively charged hydrogen ions are present in these metals cannot be answered exactly by resistance measurements. However, there are other reasons to suppose that dissolved hydrogen forms ions in other metals also.

THE EFFECT OF THERMIONS AND OTHER PHYSICAL PROPERTIES

It has long been known that the physical properties of metals, especially of those of Class 2, are considerably changed by taking up hydrogen.

Atoms of gases and vapors are ionized by the fields of atomic and image forces on heated surfaces and under certain conditions leave them in the form of ions. Catalytic processes, especially those of hydrogenation, ordinarily take place at higher temperatures because they are nearly always exothermal and thus lead to a rise of temperature at the surface. Hence conditions are often such as lead to the ionization of certain atoms. It is therefore important in elucidating the mechanism of hydrogenation to know the conditions at which the different atoms are ionized.

Kunsman deduced from his investigations the general rule that an element is evaporated at a surface in the form of an ion only when the work function of an electron, ϕ, is greater than the ionization potential, P, of the element, where ϕ and P represent work per mole (102).

The experiments of Langmuir and Kingdon (103) with tungsten wires in an atmosphere of cesium, conform to this rule. These investigators found that a tungsten wire which is heated to 1200°C. or higher in an atmosphere of cesium will convert *all* atoms of cesium which strike the wire into ions, which leave the surface as such.

Now the ionization potential, P, of atomic cesium is 3.88 volts and is therefore, according to the above rule, smaller by 0.65 volt than the work function, ϕ, of the clean tungsten surface, which amounts to 4.53 volts. The rule therefore establishes that the reaction

$$\overline{\mathrm{Me^+}} + \mathrm{A} = \overline{\mathrm{Me}} + \mathrm{A^+} + Q \qquad (17)$$
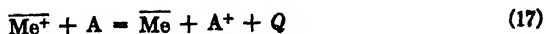
takes place from left to right only when Q has a positive value. $\overline{\mathrm{Me^+}}$ here means a surface with affinity for electrons.

Eggert (104), Meg Nad Saha (105), and finally Langmuir and

Kingdon (106) have shown that the degree of thermal dissociation of a gas, which follows the equation:

$$A^+ + \bar{e} = A + P$$

can be calculated from the ionization potential, P, by using the Nernst theorem.

The exact equation of the third principal heat theorem can be written:—

$$\log K_p = -\frac{U}{4.571\,T} + \Sigma\,\nu\,2.5\log T + \Sigma\,\nu j \tag{18}$$

if only monoatomic gases take part in the reaction (107). Here $U = P$, $P_{cal} = V\,23,028$, $\Sigma\nu = 1$, $\Sigma\nu j = -6.483$, because

$$j_e = -1.587 + 1.5\log M_{electron}$$

As $K_p = K_c \cdot RT$, $R = 0.082$ liter atmosphere, we find

$$\log K_c = -\frac{P}{4.571\,T} + 3/2\log T - 6.483 + 1.086 \tag{19}$$

If we convert from the number of gram molecules per liter to the number of atoms per cubic centimeter, i.e., so that

$$K_n = \frac{n_e \cdot n_p}{n_a} \tag{20}$$

where n_e, n_p, n_a are the number of electrons, positive ions, and atoms in a cubic centimeter, we find:

$$\frac{K_c \cdot 6.06 \cdot 10^{23}}{10^3} = K_n; K_c = \frac{K_n}{6.06 \cdot 10^{20}}$$

$$\log K_n = -\frac{P}{4.571\,T} + 3/2\log T + 15.385 \tag{21}$$

To determine the degree of thermal dissociation $n_p\,n_a$, we calculate n_e by using Richardson's equation

$$I = AT^2\,e^{-\frac{b}{T}}$$

where $A = 60.2$ amperes per cm^2. degree^2, and $b = 52,600$ for tungsten.   The density of electrons, n_e, in a volume with walls of the metal concerned is:

$$n_e = \left(\frac{2\pi m}{e^2 kT}\right)^{1/2} \times I = 4.034 \times 10^{13} \frac{I}{\sqrt{T}} \tag{23}$$

This gives for tungsten at 1200°C., $n_e = 9.25$.   Now the degree of ionization, $\frac{n_p}{n_a}$, may be calculated from equations 21 and 23.

Langmuir and Kingdon (106) found that for cesium on a surface of tungsten at 1200°K. and at a pressure of 0.001 bar, the value of the above fraction is 577:1; that is, 99.8 per cent of the cesium atoms which strike the surface are ionized.   This is an experimental value.   Under the same conditions the fraction for H^+/H would be 1.7×10^{-38}, and for H_2^+/H_2 would be similar.   Therefore under these conditions no measurable emission of H_2^+ and H^+ can be obtained.   Contrary observations by Hüttemann (108) are incorrect, as I was able to show (80).

The phenomena at the surface of platinum and tantalum are similar because the values of ϕ are in the neighborhood of that for tungsten.

From equations 20 and 21 we obtain:

$$\log \frac{n_p}{n_a} = -\frac{P}{4.571\,T} + 3/2 \log T + 15.385 - \log n_e \tag{24}$$

From equations 24, 22, and 23 we have:

$$\log \frac{n_p}{n_a} = \frac{\phi - P}{4.571\,T} + 1.779 - \log A$$

Because the last two members of this equation are practically identical for $A = 60.2$ amperes per cm.^{2} degree,^{2} i.e., for the cleanest metal of the second class, we find:

$$\frac{\phi - P}{RT} \tag{25}$$

a result which Beeker has obtained by a quite different method (109).   Thus for $\phi = P$, we get $n_p = n_a$.   But if the ionization

potential surpasses the work function by 1 volt, the fraction $\frac{n_p}{n_a}$ amounts to 5×10^{-7} at 800°A., i.e., of 10^8 atoms there are only fifty ionized. Kunsman's rule is therefore theoretically justified, but it is not an exact expression of the phenomena.

Equation 25 gives the composition of the gas phase beyond the sphere of the image forces.

From the experiments of Coehn and his coworkers the conclusion must be drawn that hydrogen, sorbed by palladium, travels with the positive current as positive ion. The energy of ionization needed for the reaction $H_2 \rightarrow H_2^+$ amounts to 15.4 volts or 354 Cal., and it is clear that this energy cannot be delivered by the simple sorption energy of H_2.

But it can be delivered by the heat of solution of the ions formed. If we consider the ionization process in the metallic solution

$$H_{2\,sol.} \rightarrow H_{2\,sol.}^+ + \bar{e}_{sol.} + Q \tag{26}$$
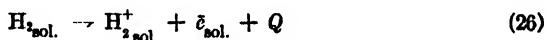
then we find by Born's cycle process:

$$Q = -A_{H_2} - I_{H_2} + S_{H_2^+} + S_{\bar{e}} \tag{27}$$
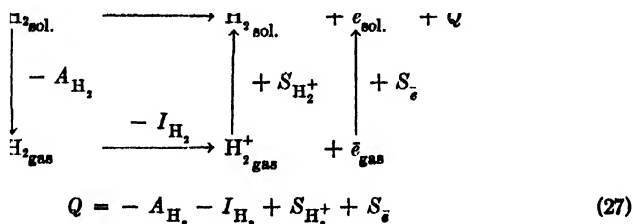
where A_{H_2} is the pure heat of sorption of H_2; I_{H_2} is the ionization potential of H_2, $S_{H_2^+}$ and $S_{\bar{e}}$ the heat of solution of H_2^+ and of $\bar{e}$. $S_{\bar{e}}$ is numerically identical with the work function, ϕ.

We set

$$Q + A_{H_2} = \tag{28}$$

where Q' is the total amount of heat produced by the process of solution of hydrogen in the metal. Then

$$Q' \qquad + S_{\bar{e}} - I_{H_2} \tag{28a}$$

As has been mentioned, Born has given a very simple method for calculating the heat of solvation, S, of an ion. He finds (8)

$$S = 1/2 \left(1 - \frac{1}{\epsilon}\right) N \times 2.388 \times 10^{-11} \frac{e^2 z^2}{r_i} \text{ Cal.} \tag{29}$$

where ϵ is the dielectric constant, N Avogadro's number, and r_i the radius of the ion. Because ϵ of those metals has a high value, we can neglect $\frac{1}{\epsilon}$. If we take, for instance, platinum, then S_ℓ is 5.5 volts, I_{H_2} is 15.4 volts and Q' was found to be 1.3 volts. That gives $I_{H_2^+} = 11.2$ volts. If we set r_i^2 0.5 Å., we get $I_{H_2} =$ 14.3 volts, which is too high.

But equation 29 is no longer valid at such small distances, as Webb has shown (9). The dielectric constant is really not a constant, but is a function of field force and temperature. It diminishes with decreasing ionic radius. Also the compression of the solvent, the electrostriction, changes the result. Therefore the values obtained by using equation 29 are too high. It is probable that the real values are in the neighborhood of 11.2 volts.

The concentration of the hydrogen ions at the surface must be extremely small. As Langmuir and Kingdon have shown (103), the concentration of ions in the sphere of image forces, i.e., at a distance of 10^{-6} cm. or less from the surface, depends on that outside this sphere and is proportional to it if the concentration is not too high. In our case the concentration of hydrogen ions in the gas phase is practically zero, as we have seen, and therefore the concentration of hydrogen ions at the surface can be neglected.

Rupp concludes from his experiments with electronic rays (81) that in the (111) plane of the nickel crystal, atoms of hydrogen are embedded at double the distance of the atoms of nickel. Also with iron we find a surface lattice of adsorbed hydrogen. E. Müller and K. Schwabe likewise concluded from their investigations on the nature of hydrogen sorbed by metals of the platinum group that the hydrogen at the surface is atomic (82). Nevertheless nickel in the crystalline form is completely inactive; the presence of atomic hydrogen on the surface, as found by Rupp, is not sufficient for hydrogenating purposes.

We therefore suppose that catalytic hydrogenation in this class is an ionic reaction in the metal phase between the ions of hydrogen and of ethylene. Ethylene adds electrons, as Loeb had found (112). We have

$$H_2^+ \rightarrow H^+ + H$$

$$C_2H_4{}^{2\bar{e}}{}_{sol.} + 2H^+{}_{sol.} = C_2H_6$$
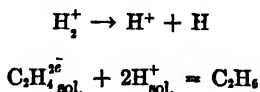
In an aqueous solution an ionic reaction usually proceeds when the product of the reaction is slightly soluble or insoluble, for example:

$$Ba^{++} + SO_4^- = BaSO_4$$
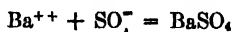
Now C_2H_6 is generally less soluble in metals than is C_2H_4, as I have found (83), and its volume is greater. By hydrogenating ethylene the distance between the carbon atoms is increased from 1.2 Å to 1.6 Å. It is therefore removed from the small pores, which are the seat of activity of the catalyst, as we shall see.

Bancroft has called attention to the fact that hydrogen ions, dissolved in water, have no reducing properties (113); therefore, according to Bancroft, a hydrogenation by positively charged hydrogen ions seems to be improbable. But in aqueous solution there is competition between the water molecules, which are dipoles of large moment, and the organic molecules, which in most cases have a much smaller moment. H^+ does not exist in aqueous solution; it forms H_3O^+. The formation of HR^+, where R is the organic compound, is quite improbable. H_3O^+ does not react as ionized hydrogen, but as a complex ion of water. Its effect is one of hydration, not of hydrogenation.

Some years ago Bonhoeffer called attention to the fact that at the surface of different metals atomic hydrogen recombines to form hydrogen molecules at different velocities (84). Arranging the metals according to their velocity of recombination gives the following series:

Pt, Pd, W, Fe, Cr, Ag, Cu, Pb, Hg
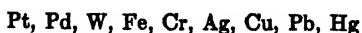
Here the elements at the left easily effect recombination, while those at the right do so with difficulty or not at all. This series

corresponds approximately to the activity of these metals as hydrogenating catalysts, except that in the above series silver precedes copper though it falls behind copper in its hydrogenating properties.

The order in which these elements show overpotential in electrolysis corresponds closely with the above. Thiel and Hammerschmidt (85) give the following sequence:

$$Pd, Pt, Ag, W, Fe, Cr, Cu, Pb, Hg$$

In this case also silver is in the wrong place from the point of view of hydrogenation.

That lead hinders the recombination of H to H_2 is easy to understand from the discussion of the stability of the PbH_4 on its surface. It protects the metal as well as the atomic hydrogen, so that no more recombination of atomic hydrogen can take place.

One may perhaps conclude that in the process of hydrogenation in the second class atomic hydrogen is the real intermediate product of hydrogenation, just as in the first class, because the elements which catalyze the process $2H \rightarrow H_2$ also catalyze the reverse process $H_2 \rightarrow 2H$. This argument seems to be obvious at first sight, but it is not conclusive. We have seen that in the solution of hydrogen in palladium there are hydrogen ions. Since ionic reactions generally proceed with infinitely great velocity, the reaction with atomic hydrogen, being one of smaller velocity, will be left behind if there is a noticeable concentration of positively charged hydrogen ions at the active points of the catalyst.

This leads to these questions: Where are the active places of the catalyst, on the visible surface or in the interior? How is it possible for the participants in the reaction to reach the points where the ions of hydrogen are located? We shall try to answer these questions by studying the events at the surface in the process of sorption.

PROCEEDINGS AT THE SURFACE IN THE PROCESS OF SORPTION; ACTIVE PLACES OF THE CATALYST

If hydrogen is taken up by metals the process of course begins at the surface; then we call it *adsorption*. The quantity of ad-

sorbed hydrogen at uniform conditions of temperature and pressure is proportional to the surface area of the body.

In the course of time hydrogen travels from the surface to the interior of the metal and at last fills uniformly the whole interior, provided the time is long or the velocity of diffusion is great enough. We call this process *absorption*. If now the extent of the surface is small in comparison with the weight of the particle, or if the solubility of hydrogen is large in comparison with the adsorption, then the quantity of absorbed hydrogen is no longer a function of the surface, but of the volume or the weight of the piece of metal.

This is shown by the experiments of Sieverts and his coworkers (86), who measured the absorption with compact pieces of metals and with sintered metallic powders and found that the quantity of hydrogen absorbed by a unit of weight of the metal between 400°C. and 1650°C. depends only on the pressure and the temperature and is independent of the surface area (87).

Between the initial state of pure adsorption, which, at low temperature and small velocity of diffusion, may be prolonged, and the final state of pure absorption or solution at higher temperatures, there are numerous intermediate states which McBain has described (88). If it is uncertain which form is involved, the process is called sorption.

If it is of importance for the hydrogenating process that the hydrogen reach the interior of the metal, this will be facilitated if the metal is porous. It is very remarkable that all hydrogenating catalysts are porous. This is especially evident with the catalyst for ammonia synthesis which is made by smelting together the lower oxide of iron and the oxides of aluminum and potassium, cooling and reducing with hydrogen; in this way pieces of metal with indefinitely many pores are obtained. As early as 1910 Bosch and Mittasch expressed the idea that aluminum oxide in this catalyst protects the finely porous structure of the iron and therefore conserves its catalytic power.

The catalysts used for the hydrogenation of organic compounds are also finely divided, porous metals. Numerous technical methods are used to obtain great porosity; one of the methods

most used is the addition of inert porous materials, such as alumina, infusorial silica, and pumice stone, in the preparation of the catalyst. These carriers are not always completely inert. Mittasch and Keunecke have shown that iron oxide and alumina form mixed crystals, which diminish the possibility of reduction and augment the activity of the catalyst (89).

One might suppose that porous catalysts are only a convenient form of procuring a mass with a very large surface. That, however, is wrong. It is true that a porous mass has an enormous surface in a small volume. A crystal of chabasite, weighing 1 g., has after dehydration an interior surface of many hundred m². But the mere area of the surface is not decisive; its form and position are also involved. We have many reasons to suppose that surfaces which are completely free from pores have no catalytic properties.

This follows, for instance, from the researches of Bredig and Allolio (90). These investigators produced a metallic surface on a carrier by dispersing platinum, palladium, and nickel in hydrogen. In the case of platinum they obtained beautifully brilliant surfaces, but all these metals in this form were inactive or nearly so. The nickel was still inactive at a temperature of 350°C. It is also well known that smooth sheets or nets of the active metals are completely inactive for hydrogenating purposes.

Taylor adheres to the view that the corners, tips, and edges of the surface are the active places of the catalyst (91). From this point of view the negative results of Bredig and Allolio are easy to understand, since the surfaces used by them were wanting in the development of corners, tips, and edges. However, the edges and tips of the exterior surface doubtless do not represent the most active points of the catalyst. There, it is true, atomic hydrogen can exist, but the ionized hydrogen can not, as we have seen.

Smekal has shown in a series of papers the importance of faults of structure in the crystal. The firmness, conductivity of electricity and heat, and the interior electric properties depend enormously on the presence or absence of such "loose places." Thus the firmness, i.e., the resistance to disruption, of an ordi-

nary crystal which has these faults, is 100 to 1000 times smaller than that of the ideal crystal. According to Smekal these "loose places" are the active centers of the interior of the crystal. In crystals composed of ions these are the points at which the ions are connected lightly and are loosened to take part in the transport of current. At low temperatures the loosened ions can be conductive ions. *These "loose places" are the active places of the catalyst.* According to this theory it is at the "loose places" of the crystals of hydrides of the alkalies and alkaline earths that the ions of these metals and H^- are loosened. Here we should expect that dissociation into Me^+ and H^- would take place when the heat vibration is sufficient. As we have seen, H^- is unstable and can easily be dissociated into H and $\bar{e}$, so that we have active forms of hydrogen at the "loose places" of these hydrides.

Especially the catalysts of the second class are characterized by their enormous content of "loose places." We must suppose that at these places free ions of the metals, with single or double charge are present, and *that the pores accessible from the outside are the really active places of the catalyst.*

IMPORTANCE OF THE SIZE OF PORES

There is no doubt that the size of the pores of solid substances has a large influence on the sorption of gases and therefore on the catalysis. The best object for studying this influence is dehydrated chabasite, as I have shown (93). Tammann has called attention to the fact that chabasite belongs to a class of minerals which remain transparent after dehydration (94). Brill has established that the lattice of chabasite is not changed by dehydration; the pores which are produced by dehydration are therefore of quite extraordinary regularity. They constitute, so to speak, a natural gauge.

Now I have shown that with inert porous sorbents, such as dehydrated chabasite, dehydrated gypsum, silicious acid, and charcoal, the sorption of a series of gases,—including hydrogen, nitrogen, carbon monoxide, argon, oxygen, methane, ethylene, ethane, carbon dioxide, and ammonia,—at constant temperature

and at a pressure of 1 atmosphere, and in a range of temperature between 0 and 150°C. follows the simple equation:

$$\log c = a \sqrt{\lambda} + b$$

where c is the sorbed volume of gas in cc. under normal conditions, λ is the heat of evaporation, and a and b are constants, which are invariable for different gases at the same conditions of temperature and pressure for the same sorbent, but vary with the conditions and the sorbents (93).

This logarithmic relation was justified by many experiments with the above sorbents and gases   Therefore it was extremely surprising that a series of gases and vapors did not follow the above equation and gave no or little sorption.   These gases and vapors were propylene, butylene, butadiene, ether, benzene, and hexamethylene.   The last three were not sorbed at all.

The results of these experiments are shown in the fourth column of table 9; in the fifth column are the calculated values, in the second the molecular volume, and in the third the diameter, σ, calculated by the usual methods.   The calculated and the observed values begin to differ notably at a fixed value of the molecular volume or diameter.   Down to ethylene, the molecular volume of which is 44, the sorption follows the formula.   But propylene, with a molecular volume of 67, gives a sorption of only 13 per cent of the calculated value.   The sorption of butylene and butadiene is only 1 per cent and that of the remaining gases is practically zero.   Ethane is at the dividing line; some sorbents give low values for it.

The reason for this phenomenon is that the pores of chabasite have fixed dimensions and therefore the molecules of gases which are too large cannot enter the crystal and cannot be absorbed.

In sorbing gases in many other sorbents, experiment and theory deviate, beginning with propylene.   The actual sorption lags increasingly behind the calculation as the molecular volume rises.   But while the sorption of dehydrated chabasite is equal to zero for gases of molecular volume greater than 90, that is not the case with the other sorbents.   Thus it is known that charcoal absorbs both benzene and ether to a large extent.   It is

easy to understand that sorbents such as dehydrated gypsum, vanadium oxide, uranium oxide, charcoal, and amorphous silicious acid do not show such a typical effect of gauge. The dimensions of their pores are not so exactly defined as in the case of dehydrated chabasite; they vary between wide limits.

If we pass from solid, porous, inorganic substances to organic colloids, such as rubber, the rigid fixation of the pores vanishes

TABLE 9

Sorption of gases by dehydrated chabasite

FORMULA	MOLECULAR VOLUME	$\sigma \times 10^9$	QUANTITY OF SORBED GAS PER 0 2 G OF DEHYDRATED CHABASITE AT 100°C. AND 760 MM.	
			Found	Calculated
NH_3	25 2	—	37.0	41.5
O_2.	28 0	29	0.6	1.5
Ar	28 3	28	0.4	1.3
H_2.	28 6	23	0 1	0 1
N_2.	34.5	31	1.2	1.0
CO	35 3	32	1.6	1.2
CO_2.	35.1	32	13.3	17 0
CH_4	33 0	28.3	1.9	2.5
C_2H_4	44.0	32 9	8.3	10 3
		36.0		
C_2H_6.	55 0	39.9	6.6	12.4
C_3H_6.	67 0	—	4.0	29.7
C_4H_6	90	—	0.8	64.4
C_4H_8	88	38.9	1.4	72 4
C_6H_6.	96	41.0	0.0	251
C_4H_9OH	102	—	0 3	407
$(C_2H_5)_2O$	107	48	0.0	126
C_6H_{12}.	117	—	0.0	251

and therefore the size of the pores does not prevent the sorption from following the logarithmic relation. I found no deviation between the observed and the calculated values for the gases sulfur dioxide, butadiene, butylene, methyl chloride, and ethyl chloride in using natural rubber.

The conclusion from these experiments is that the sorption in porous materials takes place especially in the pores and that the

ratio of the diameter of the pores to the diameter of the gas molecules is of decisive influence on the sorption and the catalytic effect.

While relatively small molecules must be considered as spherical, organic molecules having a long chain of carbon atoms show a quite different behavior. This becomes evident in the hydrogenation of organic chain molecules containing a $C{=}C$ bond. Here the position of the double bond in the chain is decisive and not the value of the molecular volume. If the double bond is in the 1, 2 position, the unsaturated compound is easily hydrogenated. So also if the molecule is large, as in the esters of undecylenic acid. In these cases the velocity of hydrogenation practically does not differ from that of small molecules such as allyl alcohol and the ester of acrylic acid. But if the double bond lies in the middle of a long chain, as in oleylic alcohol, the ester of oleic acid, and elaidic acid, the reaction velocity is less by about two powers of ten (25) for nickel as catalyst.

The explanation of these phenomena on the basis of our theory is that it is necessary for the reaction group to enter into the pores, and that for mechanical reasons this is easier when the double bond is at the end of the molecule.

The pores, but not the tips and edges of the exterior surface, are the reactive points of the catalyst. We identify the small pores with the "loose places" of Smekal.

OTHER PHENOMENA OF SORPTION; EXCEPTIONAL POSITION OF HYDROGEN

We have seen that the sorption of gases by porous bodies and solid colloids such as rubber is given by the logarithmic relation

$$\log c = a \sqrt{\lambda} + b \qquad (4)$$

Passing from solid colloids to liquids, every resistance to the penetration of gas molecules has vanished and we must suppose that our equation is exactly valid. Indeed we find that in alcohol there is in most cases excellent agreement between theory and experiment, using the data given by Carius (95). (Figure 5-1.)
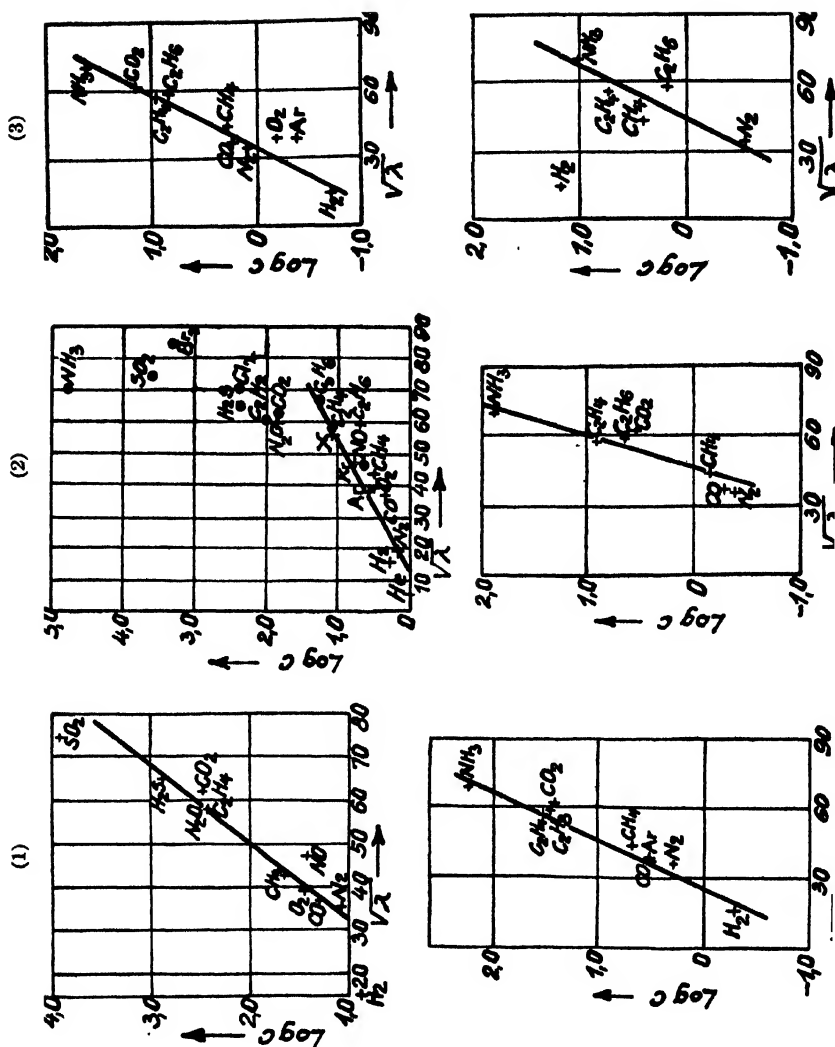
FIG. 5. RELATION OF SOLUBILITY AND SORPTION OF GASES TO HEATS OF
EVAPORATION

1. Solubility in 100 cc. of alcohol at 20°C. and 760 mm.
2. Solubility in 100 cc. of water at 20°C. and 760 mm.
3. Sorption by 0.2 g. of chabasite at 100°C. and 760 mm.
4. Sorption by silicic acid at 40°C. and 760 mm.
5. Sorption by charcoal at 20°C. and 760 mm.
6. Sorption by 10 g. of powdered nickel at 20°C. and 760 mm.

But the sorption in water, calculated with data from the tables of Landolt-Börnstein, in many cases gives large deviations from the theoretical values, as is shown in figure 5–2. In this case only the noble gases and the mono-olefins follow the logarithmic relation exactly, while all those gases which form ions in water, such as carbonic acid, ammonia, hydrogen sulfide, and sulfurous acid are excessively sorbed, the excess increasing with the concentration of ions in the solution under the conditions of the reaction. Nitrous oxide and the halogens also show a large increase of the constants. Nitrous oxide and the halogens are among the gases which easily add electrons (96).

It is this facility in adding negative charges which explains the increase of the sorption constants in the case of water. In the case of gases which give ions on solution, the energy of the van der Waals' forces of attraction is augmented by the energy of hydration of the ions produced by forces of Coulomb's attraction; therefore we have an exaltation.

SORPTION OF GASES BY METALS

My investigations of the sorption of gases in metals have given the following results. Metals of the second class show a great increase in the sorption of hydrogen, which in the case of nickel is more strongly absorbed than ammonia. This increase of sorption is much greater, indeed of another order of magnitude, than the small increase which often occurs with hydrogen and can be explained by the small diameter of its molecule. Mixtures of iron and nickel gave a smaller increase than did nickel alone. The sorption of the other gases follows the logarithmic relation, as is shown in figure 5–6.

The sorption of hydrogen is quite normal with aluminum and silver, which are not catalysts and do not belong to the second class.

With regard to the increased sorption of ionizable gases in water and the large sorption of hydrogen in nickel, we conclude by analogy that hydrogen is ionized on solution in nickel. Then the situation in nickel is the same as in palladium, where the existence of ionized hydrogen was established.

OTHER THEORIES

Hedwall and his coworkers have advanced the view that the ability of a crystallized material to react reaches a maximum at temperatures at which the material suffers crystallographical changes (97). Ch. Slonim showed that the transition of one type of crystal into another goes through the amorphous state (98). These transitions therefore involve intermediate forms, the energy content of which is larger than of the crystals.
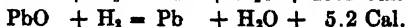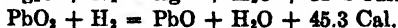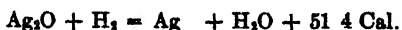
In the transition state some substances show a maximum of catalytic activity, as Hüttig and Brühl have found (99). Therefore one may assume that the finely divided state of some active catalysts is the cause of their activity, since they are in this state of transition and the heat of the change from one type to the other furnishes the necessary energy of activation.

It seems probable that this heat of change can not be neglected in the interpretation of the mechanism of the process of hydrogenation, but it is certain that it cannot explain the real activation, for the hydrogenating catalysts, e.g., that of the ammonia process, are not amorphous but are crystallized and endure a very long time. It is very improbable that the heat of change can be of great importance in such a catalyst.

B. THE HYDROGENATION OF MULTIPLE BONDS BETWEEN CARBON, OXYGEN, AND OTHER ELEMENTS

The catalysts which are able to hydrogenate the multiple bonds of carbon are not always the same as those which hydrogenate the multiple bonds between carbon and other elements. Thus, for instance, copper is an excellent catalyst for the hydrogenation of the $C=O$ bond but it is unable to effect the hydrogenation of the $C=C$ bond in stilbene and of the aromatic bonds in benzene, toluene, etc. (100). Furthermore, Brown and Henke have shown (101) that aromatic compounds containing nitro groups, such as nitrobenzene and nitrotoluene, can be reduced to the amines with good yields by hydrogen with the use of lead and silver as catalysts. Yet in the hydrogenation of the multiple bonds of carbon, lead is a poison and silver is completely inactive.

Only such metals are able to reduce nitro compounds as have oxides which are reduced by hydrogen with the development of heat.

$$Ag_2O + H_2 = Ag + H_2O + 51\ 4\ Cal.$$
$$PbO_2 + H_2 = PbO + H_2O + 45.3\ Cal.$$
$$CuO + H_2 = Cu + H_2O + 20.1\ Cal.$$
$$PbO + H_2 = Pb + H_2O + 5.2\ Cal.$$

That is easy to understand, for when absorption of heat is involved the reduction of the metallic oxides is no longer possible under normal conditions of reaction. Therefore the metallic catalysts would go over irreversibly into the inactive oxides.

In this case, too, the metal is the catalyst; but as intermediate product we find here a metal oxide, if the nitro group is reduced. It is probable that the nitro group gives its two oxygen atoms to the catalyst in forming the radical, $C_6H_5N:$, which is then reduced to aniline. However, the manner in which this reduction takes place is doubtful at this time.

The $C{=}O$ bond is hydrogenated either by conserving the oxygen in the molecule or by eliminating it. Of the metals, copper, nickel, cobalt, the oxides of which are reduced with development of heat, copper is the most effective because it gives the highest heat value (20.1 Cal.), while nickel and cobalt often reduce oxygen compounds to hydrocarbons, for instance C_6H_5CHO to $C_6H_5CH_3$ (101).

It is easy to understand that copper is especially able to conserve the $C{=}O$ binding. The large development of heat in the reduction of its oxide with hydrogen shows that the firmness of the binding between oxygen and metal is here less than in the above metallic oxides and also smaller than that of the bond between carbon and oxygen.

The affinity for oxygen of the active metals therefore decides the course of the process.

SUMMARY

The mechanism of catalytic hydrogenation of *multiple carbon bonds* is as follows:

The active elements, which act essentially as such, are divided into two classes.

To the first class belong mono- and bi-valent elements, including the alkalies and alkaline earths, which form stable, solid, salt-like hydrides. These elements are at the maxima of the long periods of the atomic volume curve, and have a large atomic volume. Their catalytic activity is small. Among the alkali metals the activity increases with the diameter of the atom. It is very probable that hydrides are intermediate products of the reaction, which then give negatively charged ions and atoms of hydrogen by dissociation in the interior of the catalyst.

To the second class belong the bivalent elements or those which have a minimum valence of 2 (Fe), or a maximum of 2 (Cu), which do not form solid hydrides but do form solutions with hydrogen, which have a small atomic volume and are "gap elements" in the periodic system. They are at the minima of the long periods of the atomic volume curve and are the more active the smaller is their atomic or ionic radius. Their ionization potential, $Me^+ \rightarrow Me^{++}$, amounts to about 18 volts and corresponds surprisingly with the work of ionization of $H_2 \rightarrow H^{++} + H + \bar{e}$. To this class belong the elements of the iron and platinum groups, and also copper, chromium, manganese, and rhenium. In the interior of these metals, when charged with hydrogen, there are positive hydrogen ions, as is proved by the experiments of Coehn and his coworkers, the phenomena of the thermionic effect, and those of sorption of hydrogen by metals.

The elements of these two classes differ markedly in their atomic volume, in the atomic or ionic radius, and in the work function. The principal properties of the two classes are quite different and the mechanism of their action must also be different.

Catalytic hydrogenation is an ionic catalysis. The ions of the catalysts,—electrons in the first class, ions of metal in the second,—are the real catalysts. In the first class the work function is small and the field of the metallic ions is weak; electrons are easily formed at the surface of the metal. Then molecular hydrogen is dissociated by the free electrons because the affinity for electrons of the atomic hydrogen favors the dissociation. It seems probable that atomic hydrogen, formed by the decomposition of hydrides, is an intermediate product of hydrogenation.

In the second class the work function is large and the field of the metallic ions is strong. In the strong fields hydrogen is ionized to form positively charged ions. Because the energy of these ions is greater than that of atomic hydrogen, it is probable that these ions are intermediate products of reaction in this class. The process of hydrogenation takes place at the "loose places" of the metal crystal or of metallic hydrides in which the ions are loosely bound. The small pores which are accessible from the outside are such "loose places" in the sense of Smekal. The mechanism of the hydrogenation of multiple carbon bonds differs from that of the C=O bond. In the latter case the affinity of the catalyst for oxygen decides the course of hydrogenation.

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